Variants of Common Nevus

5.1 Introduction

Flat, Unna, and Miescher nevi vary widely. We will consider these variants together here, but some of them should be probably considered as entities sui generis. It is advantageous to know not only the major variants of melanocytic nevus but also the unusual ones. One always has to consider the possibility that if a nevus cannot be characterized, it may be a melanoma.

5.2 Nevi with Mixed or Intermediate Phenotype

Many nevi have intermediate features and one cannot decide a clear-cut classification. Some cases with a papillated, exophytic contour would be diagnosed as Unna nevi but involve the reticular dermis (as in Miescher nevi).

These intermediate or indeterminate forms are frequently seen on the scalp and back but can be found everywhere. A large portion of these cases is probably acquired nevi resembling small congenital nevi.

5.3 Acquired Nevus with Congenital Features

Flat nevi and Unna nevi are acquired lesions, which can have features usually considered hallmarks of a congenital lesion (Fig. 5.1). The lesional cells are gathered around folliculosebaceous or eccrine structures and are aligned in as cords and strands in the deep dermis. The most specific aspect of such lesions is the presence of nests within epithelial adnexal structures themselves (Sowa et al. 2008).

The nature of these lesions, which appear during the first years of life or during adolescence, is controversial. Some authors suggest that the nevi are authentically congenital and posit that only the pigment (which renders them visible) is acquired. An alternative possibility is that they are acquired but evolve from perineural melanoblasts that ascend to colonize the dermis and its adnexa. Unlike large congenital nevi, which usually have initiating mutations in n-ras, both small nevi with a congenital pattern and small, acquired common nevi most often have initiating mutations in b-raf.

In our experience, this type of nevus is the type most often associated with melanoma in Caucasian patients. The melanomas that arise in these nevi develop at the junctional zone of such lesions in adult life and, like the nevi that they arise in, carry a b-raf mutation (Wu et al. 2007).

5.4 Lobulated Intradermal Unna Nevus

These lesions are mostly congenital, but acquired forms are reported as well (Kim et al. 2011). They feature (Fig. 5.2) an exaggerated, giant version of the exophytic papillae of Unna nevus, probably as a consequence of aging (lesions are reported as long lasting for 20–40 years). The different clinical patterns have been described as corymbiform, raspberry- or cauliflower-like, or verrucous. All the reported patients are women. Histologically, the most striking finding (which also raises the suspicion of nevoid melanoma) is solid-appearing masses of dermal melanocytes. Reassuring features are fibrosis, fatty metaplasia, and schwannian maturation. Mitoses are inconspicuous as are the cytological details.

5.5 Nevus with Metaplastic Ossification (Nanta Osteonevus)

Foci of ossification can be scrutinized within the dermal component of a nevus (1.4% of nevi in routine work). The patients are nearly always women with an average age of 46 years (Al-Daraji 2007), and the lesions in question are located on the face. There are no clinical findings that make finding bone microscopically more likely. As the nevi in question are usually Miescher, this variant is not really a type of nevus but a histological detail.

The inclusion is a small roundish mass of lamellar or structureless bone. In some cases, adipocytes may be found in the center of the bony deposit, and exceptionally, there are marrow elements (Fig. 5.3). A thin rim of osteoblasts is

G. Massi and P.E. LeBoit, *Histological Diagnosis of Nevi and Melanoma*,
DOI 10.1007/978-3-642-37311-4_5, © Springer-Verlag Berlin Heidelberg 2014

present around the bony mass.

Ossification is thought to be the result of folliculitis provoked by the nevus, leading to a small roundish scar, in which the bone develops. A ruptured infundibular cyst can also produce the same result and extruded corneocytes can sometimes be found around the bone. Ossification has also been described in Spitz nevus and in melanoma.

5.6 Nevus with Mucin

Variable amounts of mucin are occasionally detected in the upper portion of a nevus (Fig. 5.4); at times, mucin deposits can be massive. How one balances one's hematoxylin and eosin staining determines how easily one sees mucin in nevi; in well-stained slides, one does not need special stains to see mucin. The connective tissue mucin in nevi stains with Alcian blue and with colloidal iron. Melanocytes inside the mucin pool are spindled or stellate but can be inconspicuous. In rare occasion mucin gathers in a central roundish pool ringed by melanocytes or can be seen in so-called pseudovascular spaces.

Mucin can also be seen in a nevus with follicular mucinosis (Perdiki and Bhawan 2008), where mucin accumulates inside a pilosebaceous unit. In these cases, there can be many lymphocytes around and in the follicular epithelium. So-called incidental follicular mucinosis seems unrelated to alopecia mucinosa or mycosis fungoides.

Edema can alter the architecture of a nevus, creating bizarrely shaped nests (Fig. 5.5). The cytological details are however unaffected and the diagnosis is usually easy. Edema is particularly common in polypoid Unna nevi; these often have a history of being traumatized by clothing.

5.7 Nevi with Trichostasis Spinulosa

In intradermal or compound nevi of the face or other "seborrheic" zones, large follicles can contain many distinct vellus hair pilar shafts. Clinically, these follicles appear as comedones from which thin, barely visible hairs protrude. This peculiar trait may be due to constriction of the infundibulum, folliculitis, and fusion with adjacent follicles.

5.8 Nevi with Cyst

In common nevi, the presence of large and dysmorphic follicles with a hamartomatous appearance is not rare. These follicles are prone to develop infundibular cysts, which are frequent in the core of a nevus or deep to it. Again, the pathogenesis may be infundibular constriction. The cyst can rupture, and when this happens, an intense inflammatory response ensues. This causes the nevus to change clinically – becoming more raised and erythematous.

The stereotypical intranevic cyst is infundibular (the cyst is lined by squamous epithelium with a granular layer and the keratin in the lumen is laminated). Occasionally trichilemmal or epidermoid cysts manifest; also hidrocystoma and steatocystoma occur inside a nevus.

5.9 Nevus with Amyloid

An ordinary nevus can contain amyloid which is probably the end product of melanocytic or keratinocytic degeneration. The amyloid consists of small pink spherules among the melanocytes. This phenomenon does not have biological or clinical consequences.

5.10 Nevus with Pseudovascular Lacunae

About 8% of nevi that either markedly expand the papillary dermis or extend into the reticular dermis have irregularly shaped, empty-appearing spaces (sometimes pale blue, containing mucin) which are interconnected to each other in a sinusoidal manner. Most nevi with pseudovascular spaces are either Unna, Miescher, or superficial congenital types. These spaces are practically unknown in Clark and Spitz nevi and in melanoma. Melanocytes form irregularly shaped papillae inside the spaces and tend to be multinucleated. The spaces can simulate lymphatic channels containing emboli of melanocytes (Fig. 5.6).

The origin of these peculiar spaces is unclear; they do not seem to be related to anesthetic injection (Demitsu et al. 1998). The spaces occur in nests that are not as well outlined by laminin as other nests in the same nevus are.

5.11 Melanocytic Nevi in Combination with Epithelial Neoplasia

Desmoplastic trichoepithelioma are too often associated with nevi (Fig. 5.7) for this to be considered fortuitous. This occurrence is most commonly seen on the faces of young women. In such cases, the lesion consists in a mixture of thin cords and strands of basaloid cells with small, monomorphous nuclei and small nests, cords, and strands of small round melanocytes. The epithelial cells are rimmed by collagenous stroma.

Other rarer associations (Fairhurst et al. 2008) of melanocytic nevi are those with basal cell carcinoma, syringoma (Fig. 5.8), or abortive pilar follicles (on palms and soles). We present here a nevus associated with eccrine syringofibroadenoma (Fig. 5.9).

5.12 Hypermelanotic Nevus

This lesion (Cohen et al. 1997) is darkly pigmented and frequently excised for its worrisome clinical appearance. Its salient characteristic is the abundance of melanin. Melanin granules are present in the basal layer where they blur the nuclear and cytoplasm details of the keratinocytes. Melanin is present in the corneocytes too, where it aggregates in small round spheres, and in flat lamellae, which simulate nuclei creating a picture of "pseudoparakeratosis." One can tape strip these lesions and see brown scales adherent to the tape. The basilar melanocytes have elongated and pigmented dendrites which insinuate themselves among the keratinocytes. Dendrites are also retained in the nests where they form a thick blackish net enveloping small, irregularly shaped, cells. Cells inside the nests are more pigmented than those disposed in single units along the basal layer. Melanocytes are mostly detectable in single units; only few nests are present. This variant of junctional nevus is similar to the so-called hypermelanotic lentigo. In some cases, small collections of small, round melanocytes are also seen in the papillary dermis.

5.13 Nevus with Neurotization

In time, melanocytes can "mature" into cells resembling Schwann cells; they are spindled and often S-shaped and are surrounded by thin, wavy, or, less often, thick and mature collagen fibers (Fig. 5.10). In the former case, mast cells and mucin appear in the clefts between the spindle cells. Cells aggregate in so-called tactoid bodies, which are very similar to Meissner tactile bodies, or corpuscles, whose cells are in a palisaded pattern. Occasionally, the nevus entirely transforms itself into a neurofibroma-like neoplasm, with virtually no recognizable nevus remnants nor pigment. Nevi are rarely entirely composed of Meissner-like structures (Kroumpouzos and Cohen 2002), with only interposed adipocytes. The silhouette of the lesion and its dimensions are the only hints of its melanocytic origins. In rarely reported cases, nerve-like structures, or Verocay body palisaded features, are reported.

Neurotization is usually seen in the lower portions of Unna and Miescher nevi and in congenital and congenital-like nevi both large and small. It is vanishingly rare in Clark or dysplastic nevi or in Spitz nevi. As the melanocytes of the first group of nevi probably evolve directly from perineural melanoblasts, and as those of the second group from epidermal melanocytes, neurotization may be a throwback to the origin of these cells.

The distinction between neurofibroma, neurilemmoma, and neurotized nevus can theoretically be made through immunohistochemistry, although it is not worth the effort. Much more important is the distinction between a neurotized nevus and melanoma with neural differentiation.

5.14 Nevus with Adipocytic Metaplasia

It is quite uncommon to find adipocytes replacing nevic tissue in the elderly (nevus nevocellularis partim lipomatodes). Melanocytes gradually decrease among the adipocytes to the point that at the end, the entire lesion looks like a lipoma (Fig. 5.11).

A peculiar form of nevus, with a prominent adipocytic component, is the so-called lobulated intradermal nevus. This acquired lesion has a clinical appearance, consisting in large vegetating lobulated masses, merging together and simulating a nevus lipomatosus of Hoffmann-Zurhelle; the melanocytes are scattered among the adipocytes. Fibrosis and neural differentiation are also present. Its congenital counterpart is pseudocutis verticis gyrata of the scalp, in which both neuroid and adipocytic metaplasia are extensive.

5.15 Traumatized Nevus

Nevi that have been excoriated, abraded, treated with liquid nitrogen, or otherwise tormented, can have features resembling those of a persistent nevus, with a scar replacing the upper part of the lesion. The scar is usually less sharply bordered than in a nevus that has been biopsied. The criteria to distinguish a traumatized nevus between a melanoma are the same as the one used in the differential diagnosis of persistent nevus (see Chap. 26). Because there was no prior biopsy, unlike the latter scenario, one cannot pull the precedent slide from the file to ensure that the lesion was initially benign. The importance of this phenomenon consists in the fact that the "scar" or the fibroplasia distorts the architecture of the nevus and is associated with the occasional enlargement of melanocytes. This entity is an important simulator of a regressing or of a "nevoid" melanoma. The change can occur in the center of a "dysplastic" or common nevus, especially one on the back (see Chap. 26).

5.16 Desmoplastic Common Nevus

As in Spitz nevus (although much less frequently), "common" nevus can also be extensively desmoplastic (Figs. 5.12 and 5.13). The few reported cases, defined by pink, lightly pigmented or flesh color, are localized on the trunk and on the proximal extremities; dermoscopically, they have a light brown network, along with a pinkish erythematous background (Ferrara et al. 2009).

Melanocytes are mostly elongated and are surrounded by abundant collagen throughout the lesion (or in a limited portion of it). Collagen fibers form onion-shaped vortices

or solid keloidal bands. Intranuclear cytoplasmic pseudoinclusions are visible, and fatty metaplasia, focal edema, and inflammatory infiltrates are reported.

Generally, the portion near the epidermis has the features of a common intradermal nevus (Miescher or superficial congenital type), which easily solves the differential diagnosis with desmoplastic melanoma.

5.17 Nevus with Nuclear Pseudoinclusions

Nuclear pseudoinclusions are common to find in all types of nevi (although they are more frequent in the deep penetrating nevus, Spitz nevus, cellular blue nevus, and melanoma). Their presence, even in abundance, is not worrisome or of value in differential diagnosis. The pseudoinclusions are due to knuckle-shaped masses of cytoplasm that invaginate the nuclear envelope.

5.18 Nevus and Actinic or Traumatic Damage

Experimentally, nevi acutely exposed to ultraviolet light show suprabasal scatter of melanocytes singly and in small nests. In a study, part of the nevus was masked, so that the sides shielded from UV light, and exposed to it could be compared. Cytologically, the melanocytes on the exposed side can be atypical with pale cytoplasm and vesicular nuclei. Immunohistochemically, the levels of HMB45 staining and of the proliferation markers PCNA and Ki-67 are similar to that seen in melanoma in situ. One of the few distinctions between the intraepidermal change in these nevi and authentic melanoma in situ is that the nuclei are very monomorphous in UV-exposed nevi. Also, from a dermoscopic point of view, these nevi seem atypical. These alterations are apparently reversible in a few weeks. Patients who easily sunburn more often have nevi with similar features.

In the routine practice, one must remember that during the summer months, nevi might frequently show junctional, irregular features with mitotic figures and a subjacent inflammatory infiltrate (the "September nevi"). Because few dermatologists are aware of this alteration, there are undoubtedly many cases of "melanoma in situ arising in a preexistent nevus" that are UV-altered nevi.

Tronnier's reproduction of these findings by tape stripping implies histopathologists should examine putative cases of melanoma in situ for signs of excoriation, such as erosion, parakeratosis with serum and neutrophils, subepidermal fibrin deposition, extravasated erythrocytes, or fibrosing granulation tissue.

While melanoma in situ and melanoma can of course be excoriated, the findings of such changes should prompt the question, "Are there findings of melanoma away from the eroded areas?" This is sometimes a question best answered by the examination of level sections.

5.19 Nevus with Foci of Altered Cornification

At times, foci of epidermal acantholytic dyskeratosis are found in the proximity of a nevus. There are clefts above the basal layer and loss of spines between keratinocytes. One may also see small zones of epidermolytic hyperkeratosis; these have pale cells in the spinous layer, coarse keratohyalin, and sometimes trichohyalin granules, with lamellar hyperkeratosis. Both of these alterations probably reflect somatic mutations in a keratinocyte stem cell, with the outgrowth of these cells colonizing a few rete ridges of the adjacent epidermis. Both alterations are common at the edges of a variety of nevi or a millimeter or so away from the nevus. They can also be present near melanomas. They are rarely found next to Spitz nevi, however. The mechanism by which a melanocytic neoplasm would induce a mutation in a keratin gene (as in the case of epidermolytic hyperkeratosis) is mysterious.

These altered forms of cornification seldom hamper the microscopic examination of the melanocytic neoplasm. Occasionally, a broad area of altered cornification will be present within the substance of the lesion and cause an asymmetric appearance. Once the alteration is recognized, the microscopist can "correct" for its presence.

5.20 Hypercellular Common Nevus

We now call "hypercellular common nevus" a compound nevus with striking cellular density (Fig. 5.14) and with very scant collagen interposed among the melanocytes.

The pattern of the lesion looks very much like a nevoid melanoma; moreover, the neoplasm is deep enough to reach the subcutis. This lesion, which can be Unna and Miescher like, is frequently found along the mammary line especially during pregnancy, but it can be occasionally seen elsewhere in patients of all ages. The erroneous diagnosis of "minimal deviation" or nevoid melanoma is frequently made or considered with such lesions.

The most important clues for a correct diagnosis are the lack of nuclear atypia and pleomorphism and the similarity between cells at each level of the dermis. While the nuclei of such lesions can be enlarged, especially in the upper part of the lesion, they are monomorphous. Changes resembling melanoma in situ are not present in such lesions. While in some similar melanomas, dermoepidermal clefts can be present due to confluence of melanocytes along the junction, such clefts are absent in hypercellular nevi unless the lesion has been traumatized.

Other findings that point to melanoma are nests that appear to compress their neighbors (expansile-appearing nodules) and melanocytes whose nuclei are diffusely hyperchromatic. In some, but not in all, hypercellular nevi, there is an up-down gradient of cellular density.

Hypercellularity is a common attribute of medium and large congenital nevi biopsied during childhood. In general, the finding of particularly dense cellularity in a melanocytic lesion in an adult should prompt careful scrutiny of the lesion for the above-mentioned changes.

There will be cases in which the examination of routinely stained sections will not suffice to resolve this differential diagnosis. The diagnosis in only a disappointing minority of cases will be resolved by immunohistochemistry, by showing either HMB45 staining throughout the lesion or a high proliferative rate in the lower part of it. Negative HMB45 staining and a low proliferation rate do not suffice to exclude melanoma, although these negative findings can be reassuring. Fluorescence in situ hybridization, comparative genomic hybridization, or other molecular testing may be necessary to arrive at a diagnosis.

5.21 Mitotically Active Nevi

While, most of the time, mitoses are absent from Miescher or Unna nevi, rarely an unusual number of them can be found in otherwise ordinary lesions. If an immunoperoxidase stain such as the one for phosophohistone H3 is used for their detection, the number can be impressive. The architectural and cytological findings are otherwise innocent and no other changes indicating melanoma are present in most such lesions. In many cases, dissociation is present between the number of mitoses and an unremarkable proliferation rate as assessed by Ki-67 staining. The reason for this discrepancy is unknown. FISH technique can be used for ruling out melanoma in these mitoses-rich benign nevi.

5.22 Nevi with Large Junctional and Intradermal Nests

Occasionally, very large nests are present inside a nevus, which in its remainder is quite banal (Figs. 5.15 and 5.16). These large nests look like the expansile nodules occasionally found in malignant melanoma. Their benign nature can be inferred by the absence of nuclear atypia, pleomorphism, and mitoses; additionally, the nevus around the nodules has an obvious innocent aspect and the large nests do not compress the other cells.

Nevi with large junctional nests need to be distinguished from what has been termed "mostly nested melanoma," in which the most reliable clue seems to be nuclear atypia. Some cases of the latter have been proven as such by microdissection, whole genome amplification, and comparative genomic hybridization.

5.23 "Ancient Nevus"

Kerl reported with this term a group of lesions that had findings reminiscent of those seen in so-called ancient neural neoplasms. In some schwannoma and neurofibroma, vascular changes and ischemia seem to result in areas in which cytologically atypical Schwann cells occur. In ancient nevi, there are two distinct components: the first is composed of conventional common nevus cells, whereas the other is characterized by large epithelioid cells with prominent hyperchromatic nuclei and prominent nucleoli (Figs. 5.17 and 5.18). These atypical cells are arranged in nodules and sheets. In this second component with atypical features, there are also histological signs of senescence like fibrosis, angiectasia, thrombi, perivascular rims of sclerosis (hyaline rings) edema, mucin, and hemorrhage. There is no junctional component.

Clinically, these are usually long-lasting lesions in elderly patients, usually on the face. Dermoscopically the ancient nevus resembles a basal cell carcinoma, a Miescher nevus, or a hemangioma.

The distinction from melanoma is usually easy because the atypical cells are few and are restricted to one nodular area of the lesion. Furthermore, the architecture of the lesion is not disturbed by such cells, which do not aggregate in confluent nests or solid sheets. The important and characteristic stromal alterations noted above are also clues to the diagnosis (Kerl et al. 2011). Occasionally the atypical details are striking and a differential diagnosis with melanoma must be carefully pondered. Genomic studies on ancient nevi have not yet been reported.

5.24 Bizarre Nevus (Nevus with "Monster Cells")

McGovern reported a relatively frequently intradermal nevus with large and pleomorphic cells (many multinucleated ones) which had large or gigantic nuclei with dark and homogeneous chromatin (Figs. 5.19 and 5.20). These melanocytic features are the consequence of senescence. According to Kerl this variant is not a genuine ancient nevus, lacking the stromal alterations typical of this entity (Kerl et al. 2011).

The lack of mitoses and nodular growth pattern helps in distinguishing this entity from melanoma. Moreover, the atypical or monster cells are evenly scattered throughout the neoplasm along with banal nevus cells. They do not form solid or expansile-appearing aggregations.

At variance with many melanomas, the nuclei have homogeneous hyperchromatic chromatin without nucleoli. Melanoma cells more often have clumped chromatin with prominent nucleoli, although diffusely hyperchromatic nuclei are found in desmoplastic melanomas.

5.25 Nevus with Eosinophilic Intranuclear Inclusion

Paramyxovirus-like inclusions have been described inside the nuclei of compound or intradermal Unna and Miescher nevi (Fig. 5.21). Whether these are truly due to viral infection is debatable (Schaefer et al. 2008). A recent paper found ubiquitin in many of the inclusions. In other occasions, inclusions are associated with a molluscum contagiosum infection. The features are bizarre indeed, but the differential diagnosis with melanoma is easy.

5.26 Nevus with "Pagetoid" Cells

This unfortunate term was coined by Ackerman to describe a junctional or compound nevus (usually of the "flat" type, Fig. 5.22) with large cells with abundant, pale, vacuolated cytoplasm and finely divided or "dusty" melanin. He used this term to note the resemblance between the cells of such nevi, and those of mammary or extramammary Paget disease. We have termed these cells pulverocytes (see Chap. 17).

While the term "granular cell nevus" has been used (El-Gamal et al. 2004), other nevi truly have granular cells, in the sense of cytoplasm packed with mitochondria, as granular cells in other parts of the body have. Ackerman contrasted pagetoid melanocytes with pagetoid spread of melanocytes, but this distinction is lost on many.

The pagetoid melanocytes in such nevi are situated at the junction or in the dermis, and there is no pagetoid spread. Large multinucleated melanocytes can be visible as well. Melanin and melanophages can be abundant. These large lightly pigmented cells can even be prevalent. The patients with this type of nevus are usually adolescents but are rarely adults.

This variant can be confused with a form of melanoma if more than an occasional atypical nucleus is found.

5.27 Balloon Cell Nevus

Balloon cell nevus is a peculiar type of compound or intradermal nevus, with massive cytoplasmic vacuolization in a substantial number of the cells (Fig. 5.23). From a clinical point of view, the balloon cell nevus is unremarkable (and this is also an important clue for the histological diagnosis) with regular pigmentation (however, entirely balloon-like lesions are often achromic).

Patients are youngsters and the favorite sites for this nevus are the head and neck (balloon cell melanocytes are found also in nevi of mucous membranes, in proliferative nodule, and in lymph nodal nevi).

Histologically, the balloon cell nevus has the architecture of an Unna nevus, being symmetrically papillated and occupying an expanded papillary dermis. Technically, most balloon cell nevi could be labeled as combined nevi (see Chap. 18).

Cytologically three types of melanocytes are seen:

- Small round melanocytes. These ordinary nevi cells can be abundant or very scarce, and in such case they are distributed at the bottom of the nevus.
- Ballooned melanocytes. These cells have an enormously expanded cytoplasm which appears empty or finely vacuolated with a sebocyte-like feature. Melanin is scarce and gathered in dusty granules. Nuclei are small and wrinkled, sited on the center of the cytoplasm. Mitoses are not found.
- Melanocytes with intermediate cytological features. These cells, which may be oncocytes, have a ground glass cytoplasm and vaguely resemble to the cells of the granular cell tumor. Some cells, similar to balloon cells, resemble sebocytes, with larger vacuoles (sebocyte-like melanocytes).

The interposed collagen fibers are undisturbed by the nevus proliferation and divide the nevus in small nests and files of cells. Balloon cell degeneration is usually associated with an ordinary nevus but can also be seen in Spitz nevus, blue nevus, congenital nevus, and halo nevus. A hyperpigmented variant of balloon cell nevus is also on record.

The most important differential diagnosis is with balloon cell melanoma. The differential diagnosis is not as simple as reported in literature and occasionally it is almost impossible; for this reason, we use the following criteria:

- Age of the patient. Balloon cell nevus is a lesion of youngsters (it usually appears before 30 years of age) while melanomas with similar features are in older patients.
- Cytological features. In the balloon cell nevus, nuclei are roundish, small, and monomorphous. Presence of a striking pleomorphism and large nuclei are indications of melanoma.
- Mitotic figures. Mitoses are never found in balloon cell nevus, so their presence strongly suggests melanoma. Unfortunately, many balloon cell melanomas have scarce mitoses or are even devoid of them and their absence cannot be taken as an indication of the benign nature of the lesion.
- Inflammatory infiltrate. The presence of a lymphocytic or lymphoplasmacytic infiltrate around the balloon cells has been interpreted as indicating of melanoma.

Besides the balloon cell melanoma, other diagnoses can be considered with similarly vacuolated cells: clear cell dermatofibroma, clear cell sarcoma, and clear cell renal carcinoma metastatic to the skin; immunohistochemistry usually solves the diagnostic dilemma. Finally, balloon cell nevus (and melanoma) can be confused with freeze-thaw artifact in which cells contain large vacuoles.

5.28 Eruptive Nevi

Crops of nevi can swiftly erupt after transplants, drug ingestion, traumas, burns, bullous diseases, or sunburns. Lesion can be numerous, with even scores of nevi occurring in rapid succession. Histologically most of them have the features of a dysplastic nevus.

5.29 Incidental Nevus

Small intradermal nevi are occasionally found in specimens of skin excised for other unrelated reasons. For example, in 372 specimen of preputial excisions for phimosis, 1.1% of the cases showed small intradermal nevi that were invisible at a clinical level (Val-Bernal et al. 2009). Often, these small nevi have a periappendageal pattern, especially in specimens of facial skin.

Because these nevi are relatively common, and the larger a specimen is, the more likely it is contain such a nevus, one must interpret their significance with caution. For instance, large patches of melanoma in situ on sun-damaged facial skin (lentigo maligna) often overlap these nevi, but small lesions seldom do. Hence, it is unlikely that lentigo maligna begins in nevi, and finding a small nevus in a large lentigo maligna should not cause that interference.

Small junctional nevi may be the cause of a phenomenon called "pseudo-melanocytic nests." These small aggregations of cells with an immunoperoxidase staining profile of melanocytes are sometimes found in lichenoid reactions on sun-damaged skin. One plausible hypothesis is that there were small, incidental junctional nevi that coincidentally encompassed in an inflammatory process.

5.30 Inverted Type A Nevus

This term is used for nevi with nests or sheets of large pigmented cells inside the dermal component, where the lymphocyte-like type B and schwannian-like type C melanocytes should be prevalent. In our opinion these are mostly combined nevi (common nevus combined with deep penetrating nevus or epithelioid blue nevus).

5.31 Further Reading

Al-Daraji W (2007) Osteo-nevus of Nanta (osseous metaplasia in a benign intradermal melanocytic nevus): an uncommon phenomenon. Dermatol Online J 13(4):16

Cohen LM, Bennion SD, Johnson TW et al (1997) Hypermelanotic nevus: clinical, histopathologic, and ultrastructural features in 316 cases. Am J Dermatopathol 19(1):23–30

Demitsu T, Kakurai M, Yamada T et al (1998) The vascular space-like structure in melanocytic nevus is not an injection artifact: report of a case and an experimental study. J Dermatol 25(3):143–149.

El-Gamal HM, Robinson-Bostom L, Saddler KD et al (2004) Compound melanocytic nevi with granular cell changes. J Am Acad Dermatol 50(5):765–766

Fairhurst DA, Merchant W, Sheehan-Dare R (2008) Admixed desmoplastic trichoepithelioma and benign melanocytic naevi. J Eur Acad Dermatol Venereol 22(3):386–387

Ferrara G, Brasiello M, Annese P et al (2009) Desmoplastic nevus: clinicopathologic keynotes. Am J Dermatopathol 31(7):718–722

Kerl H, Wolf IH, Kerl K et al (2011) Ancient melanocytic nevus: a simulator of malignant melanoma. Am J Dermatopathol 33(2):127–130

Kim DH, Park HS, Paik SH (2011) Four cases of lobulated intradermal nevus: a sign of aging melanocytic nevus. Ann Dermatol 23(1):115–118

Kroumpouzos G, Cohen LM (2002) Intradermal melanocytic nevus with prominent schwannian differentiation. Am J Dermatopathol 24(1):39–42

Perdiki M, Bhawan J (2008) Mucinous changes in melanocytic nevi and review of the literature. Am J Dermatopathol 30(3):236–240

Schaefer JT, Nuovo GJ, Yen TS et al (2008) Prominent eosinophilic intranuclear inclusions in melanocytes of a melanocytic nevus: the aftermath of an infection with molluscum contagiosum? A case report. J Cutan Pathol 35(8):782–788

Sowa J, Kobayashi H, Ishii M et al (2008) Histopathologic findings in Unna's nevus suggest it is a tardive congenital nevus. Am J Dermatopathol 30(6):561–566

Val-Bernal JF, Val D, Garijo MF (2009) Clinically unapparent melanocytic nevi on the prepuce. J Cutan Pathol 36(4):444–447

Wu J, Rosenbaum E, Begum S et al (2007) Distribution of BRAF T1799A(V600E) mutations across various types of benign nevi: implications for melanocytic tumorigenesis. Am J Dermatopathol 29(6):534–537

5.32 Summary

- A great number of nevi are reported as variants of common nevus. Many of them should be probably considered as entities sui generis.
- The histological variants more prone to be a diagnostic challenge are desmoplastic nevus, hypercellular nevus, ancient nevus, bizarre nevus, and balloon cell nevus.
- These variants must be differentiated from their malignant counterparts:
  - Desmoplastic nevus versus desmoplastic melanoma
  - Hypercellular nevus versus nevoid melanoma
  - Bizarre nevus versus nodular melanoma
  - Balloon cell nevus versus balloon cell melanoma

Fig. 5.1
Acquired nevus with congenital features

*The large diameter of the lesion (**a**) and melanocytic adnexotropism (**b**) are findings that point to the congenital nature of this lesion. These findings are utterly nonspecific and similarly occur in acquired nevi.*

In this case there are also hints of Clark dysplastic nevus: the junctional nests are irregular in size and shape. Their bases are enveloped by collagen fibers, in a pattern that can be called concentric fibroplasia

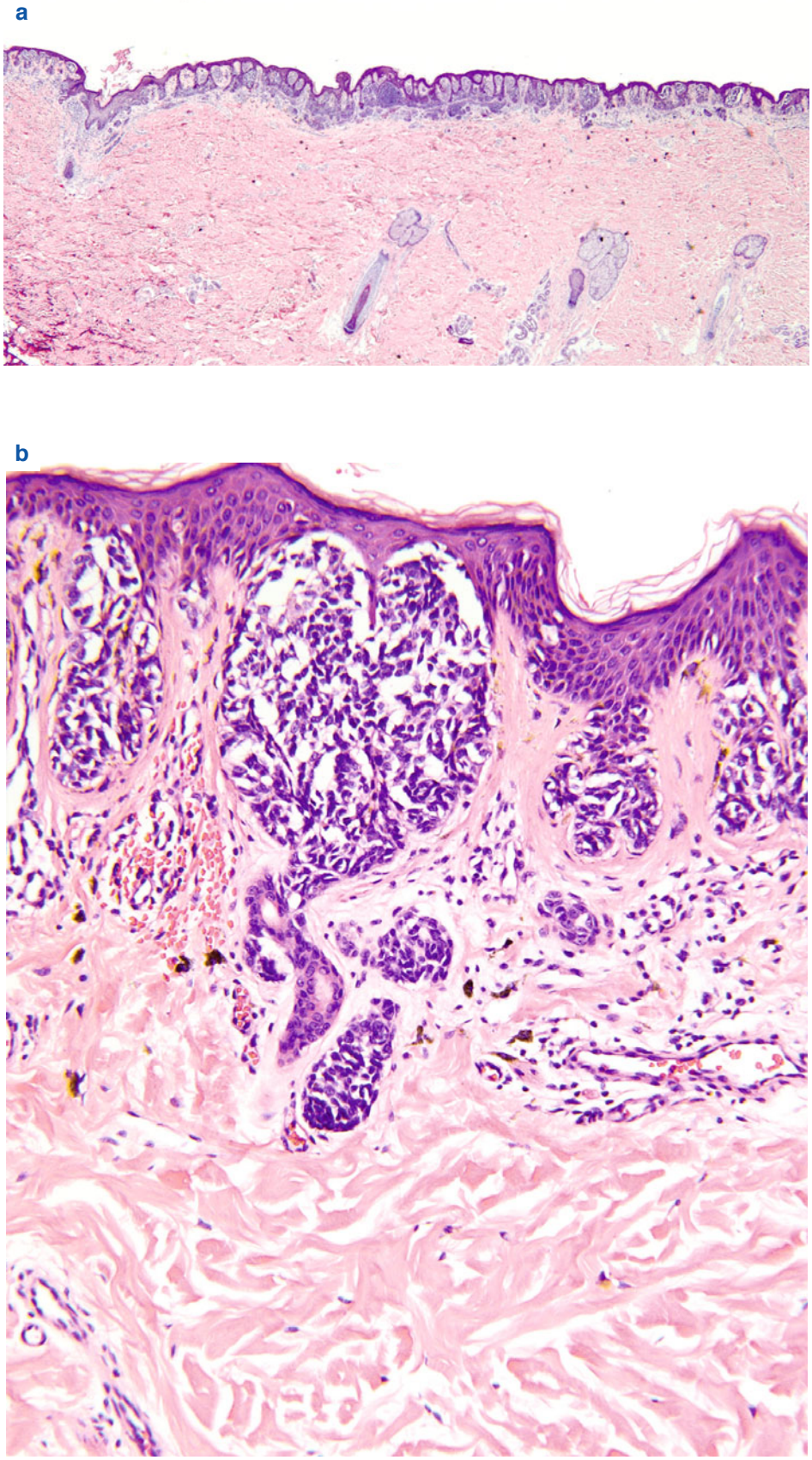
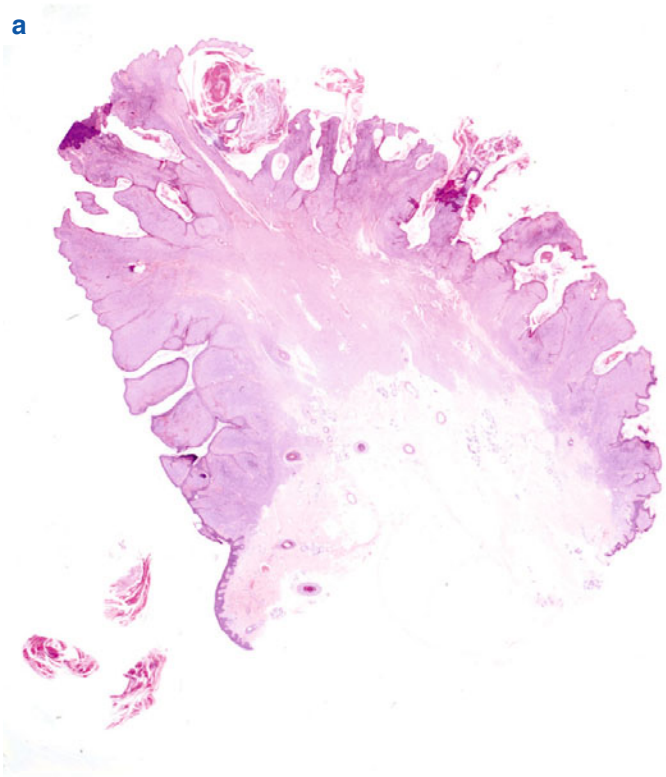


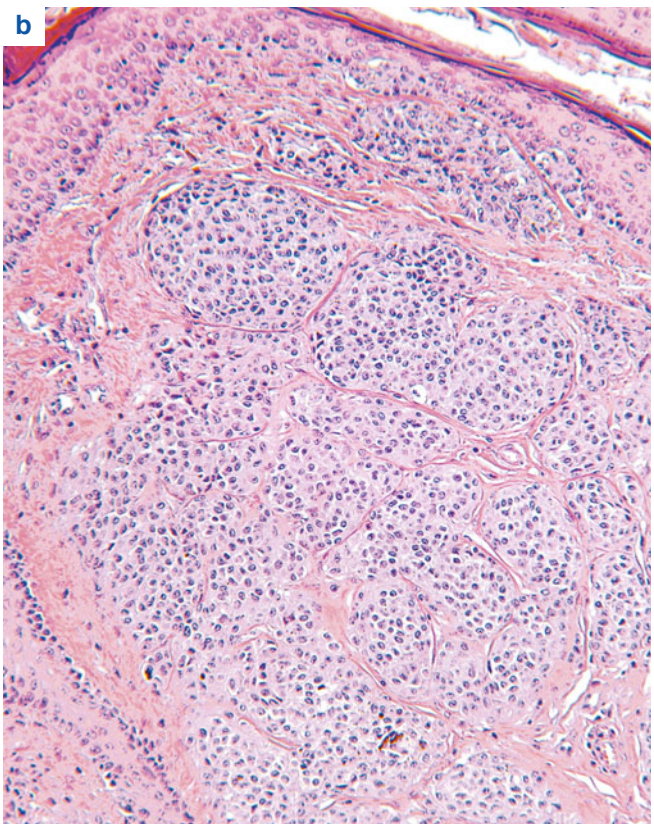
Fig. 5.2
Lobulated intradermal Unna nevus

*This gigantic example of a papillated Unna nevus (**a**) is frequently excised after years of growth, mostly for cosmetic reasons.*

*At a cursory examination, the lesion seems benign, but some architectural details deserve close scrutiny: within the top layer of the neoplasm, cells are packed together in solid sheets (**b**), like those of a nevoid melanoma, and some of the dermal nests are confluent. Moreover, a few mitotic figures are an inevitable finding in such a large nevus.*

*In cases like this, scrupulous examination of cytological details (**c**) is mandatory for ruling out a nevoid melanoma. Also, an even gradient along which cells and their nuclei diminish in size toward the base of the lesion is the rule in such nevi*





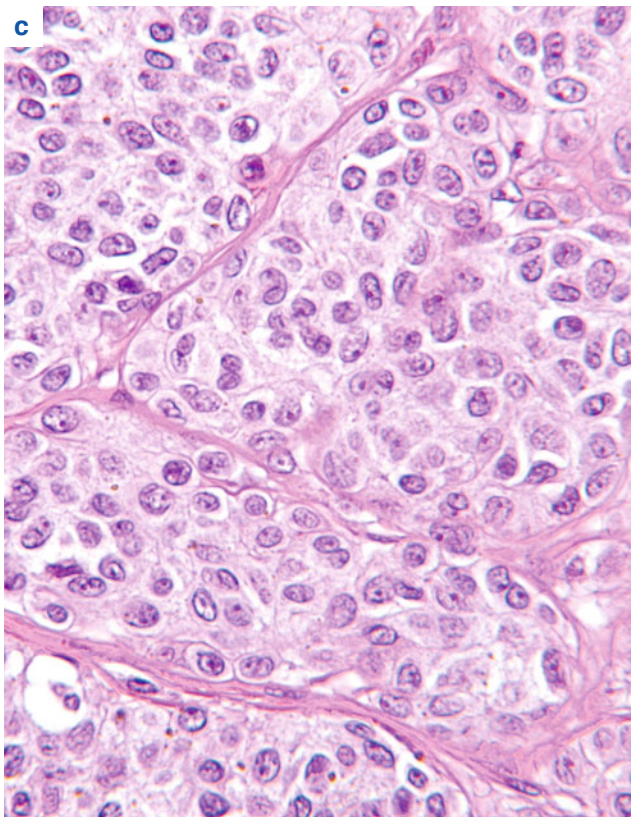
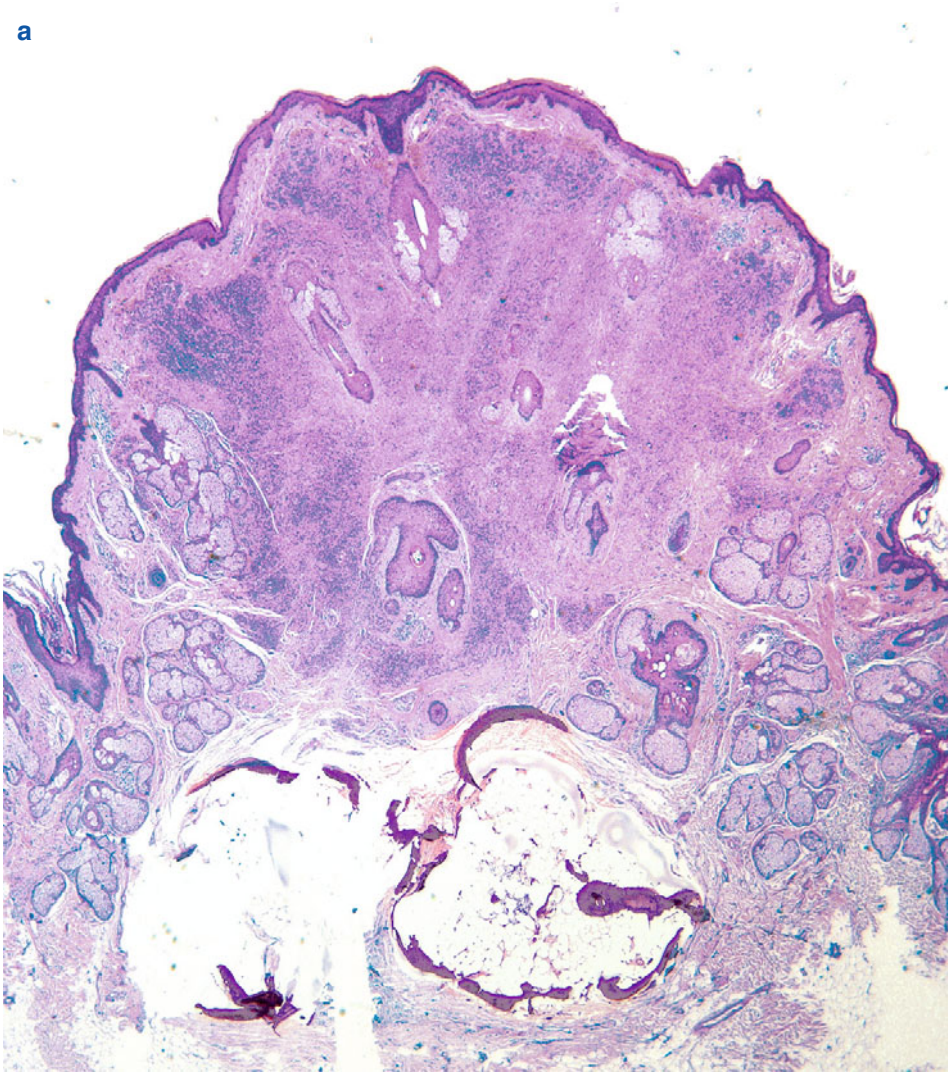


Fig. 5.3
Nanta osteonevus

*Bone trabecula can occur in the deep portion of a nevus (**a**), frequently inside a scar or in fibrosis adjacent to the residuum of a ruptured infundibular cyst. In this case some vestigial bone marrow elements are also present (**b**)*



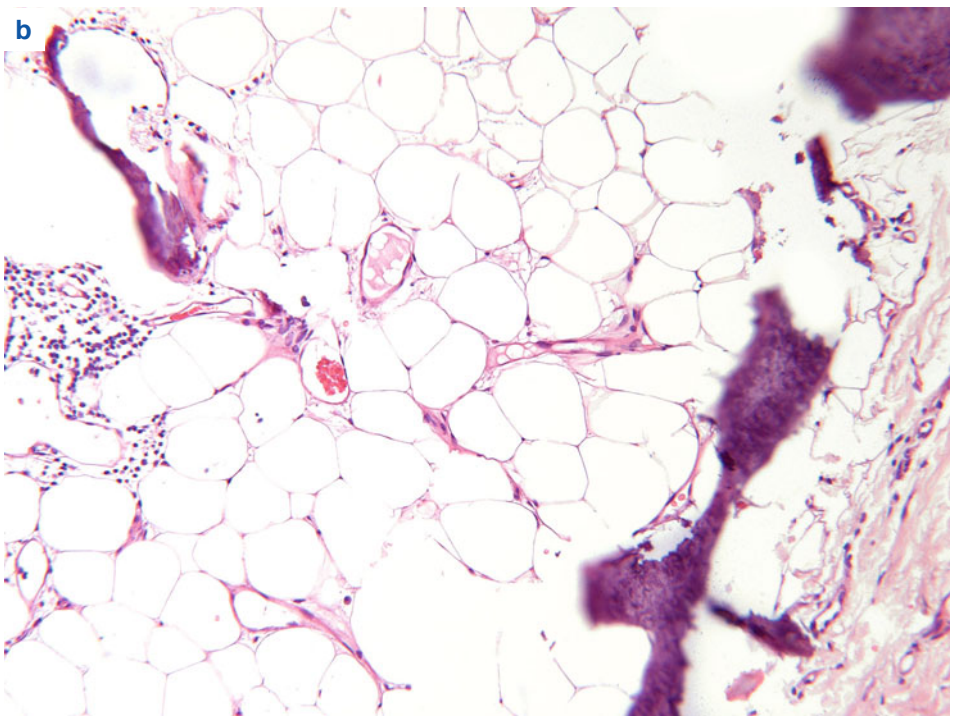


Fig. 5.4
Nevus with mucin

*The dermal cells of this Unna nevus (**a**) are focally arranged in a cribriform pattern. Inside the pseudoglandular or pseudovascular spaces (**b**), hematoxylin stains a small amount of mucin (**c**), better seen with special stains.*

Note that at the right side of the lesion is a cystic follicular infundibulum containing keratin, a structure that could rupture, changing the appearance of the nevus.

*The bizarrely reshaped dermal nests should not be the cause of confusion with melanoma: the cytological details remain perfectly innocent (**c**)*

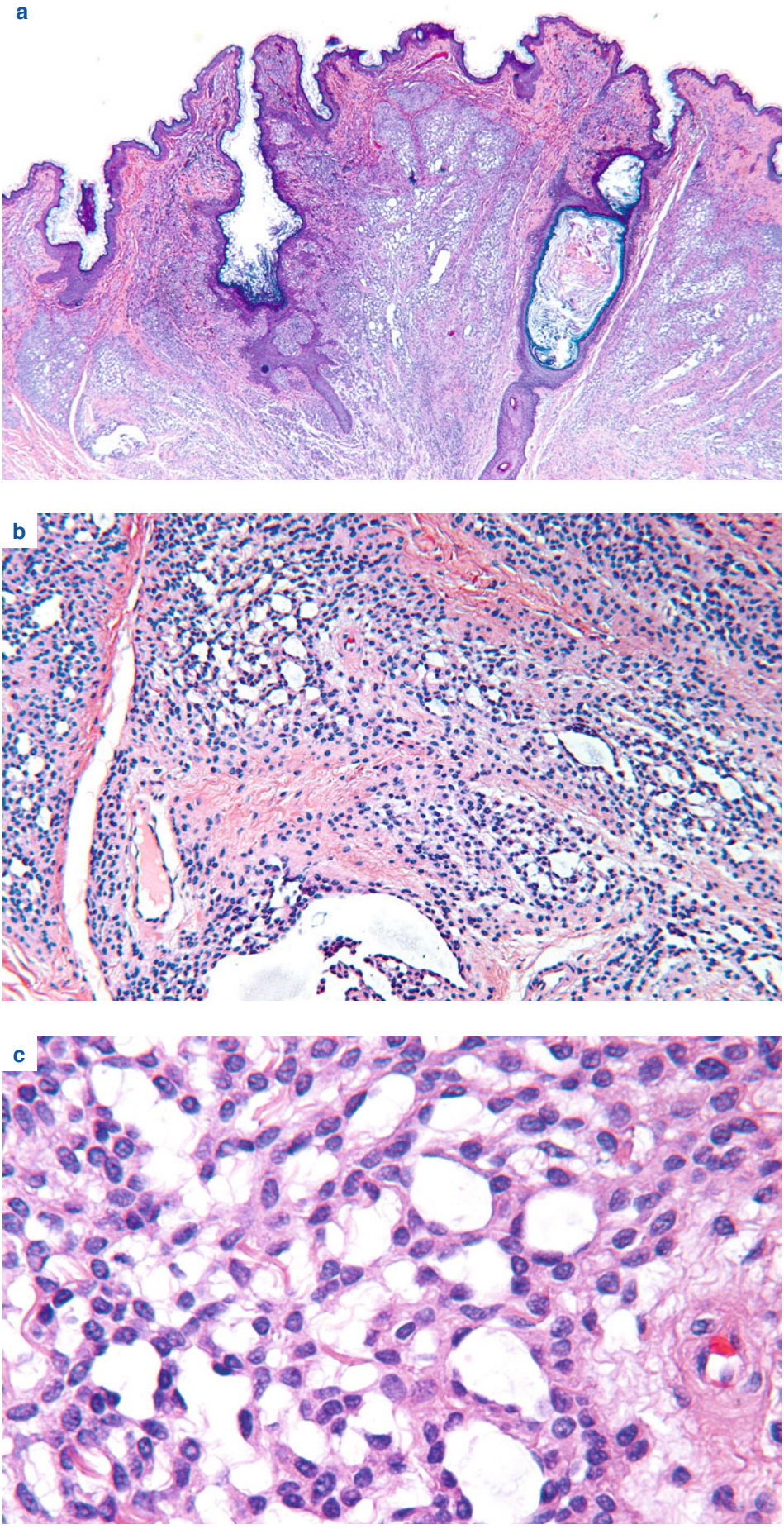


Fig. 5.5
Miescher nevus with edema

*Two large hemorrhagic pools are evident at both sides of this scanning photomicrograph (**a**). The congested lesions are also characterized by intense edema (**b**) which splays apart the aggregates of melanocytes.*

*The bizarrely reshaped dermal nests should not be the cause of confusion with melanoma: the cytological details remain perfectly innocent (**c**)*

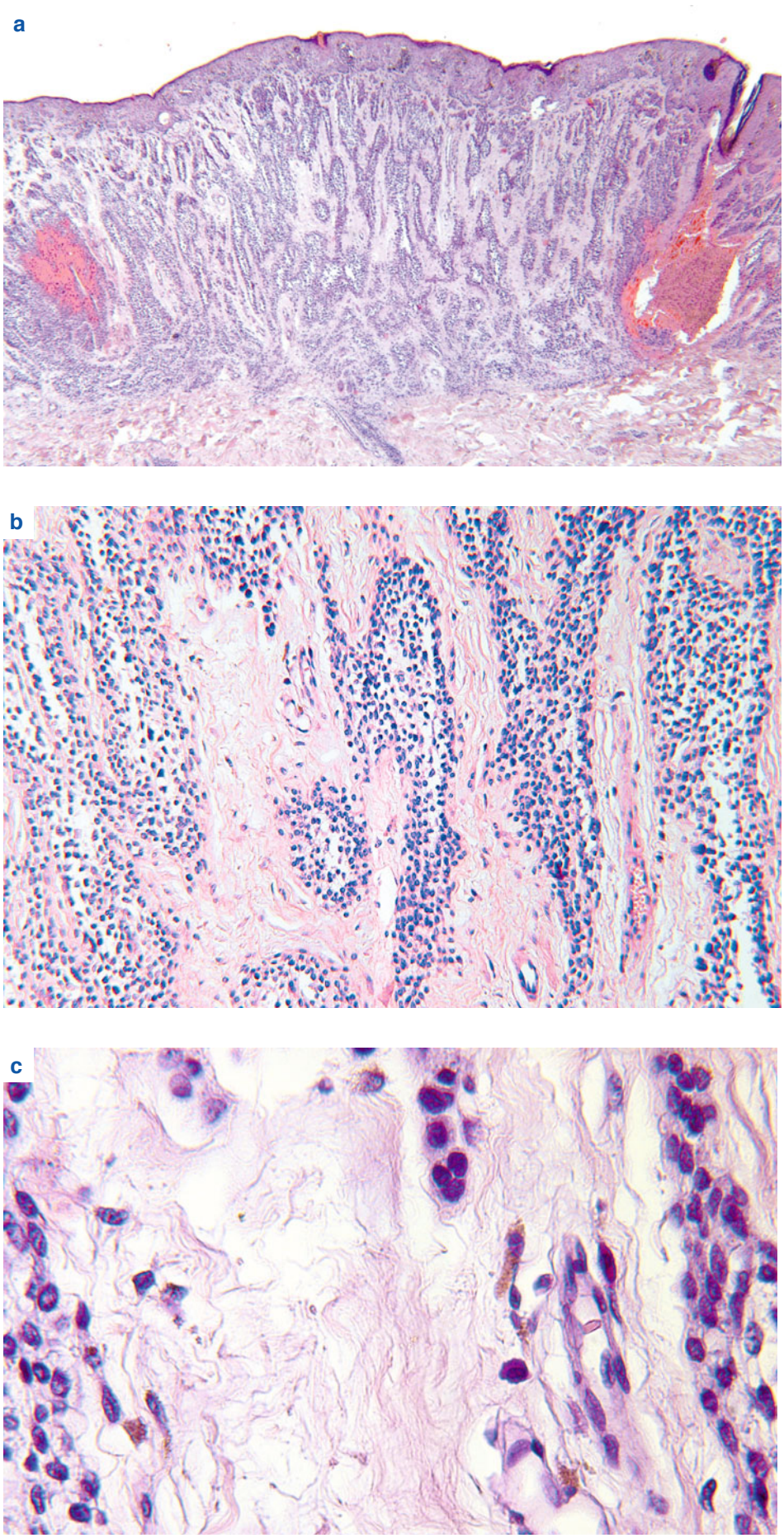


Fig. 5.6
Miescher nevus with pseudovascular lacunae

*The presence of large irregularly shaped empty-appearing spaces is not a rare finding in a common nevus (**a**); occasionally this bizarre appearing phenomenon is striking and could simulate a vascular neoplasm combined with the nevus (**b**).*

*Also, a lacelike pattern with melanocytes arranged in thin strands interconnected to each other is sometimes prominent (**c**). The described alterations are artifactual and do not constitute a sign of malignancy.*

Special stains for mucin were negative and a form of nevus with mucin can be ruled out

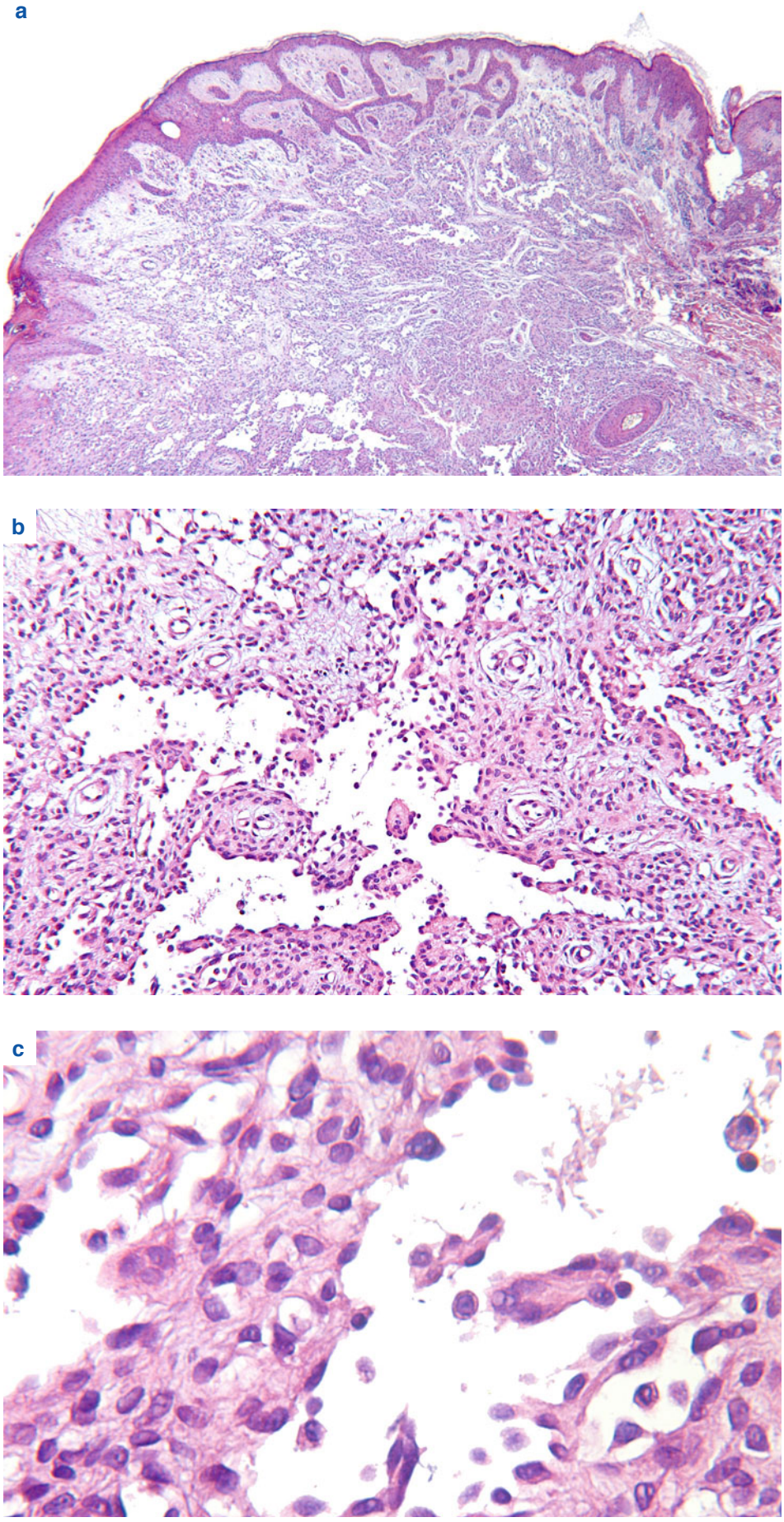


Fig. 5.7
Miescher nevus combined with desmoplastic trichoepithelioma

*This seemingly confused neoplasm is a combination of a common intradermal nevus and the peculiar follicular proliferation known as desmoplastic trichoepithelioma (**a**). The latter is composed of elongated tracts of basaloid epithelial cells (**b**) inside which small keratinous cysts can develop; nests of melanocytes find their place between the epithelial cords in a labyrinthine array (**c**).*

While desmoplastic trichoepithelioma is almost always found on the face, like the Miescher nevi with which they are found admixed with, the concurrence seems more than random

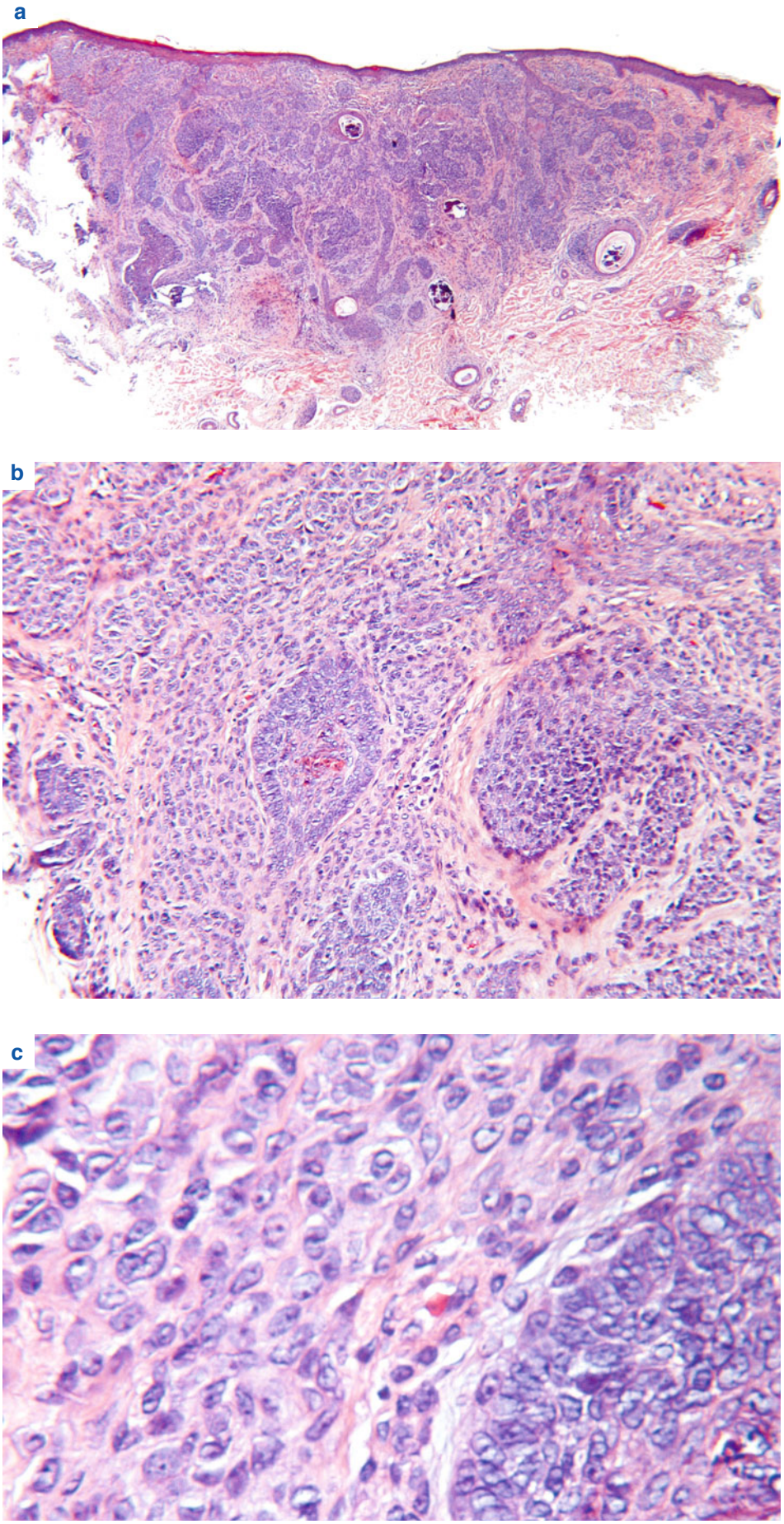
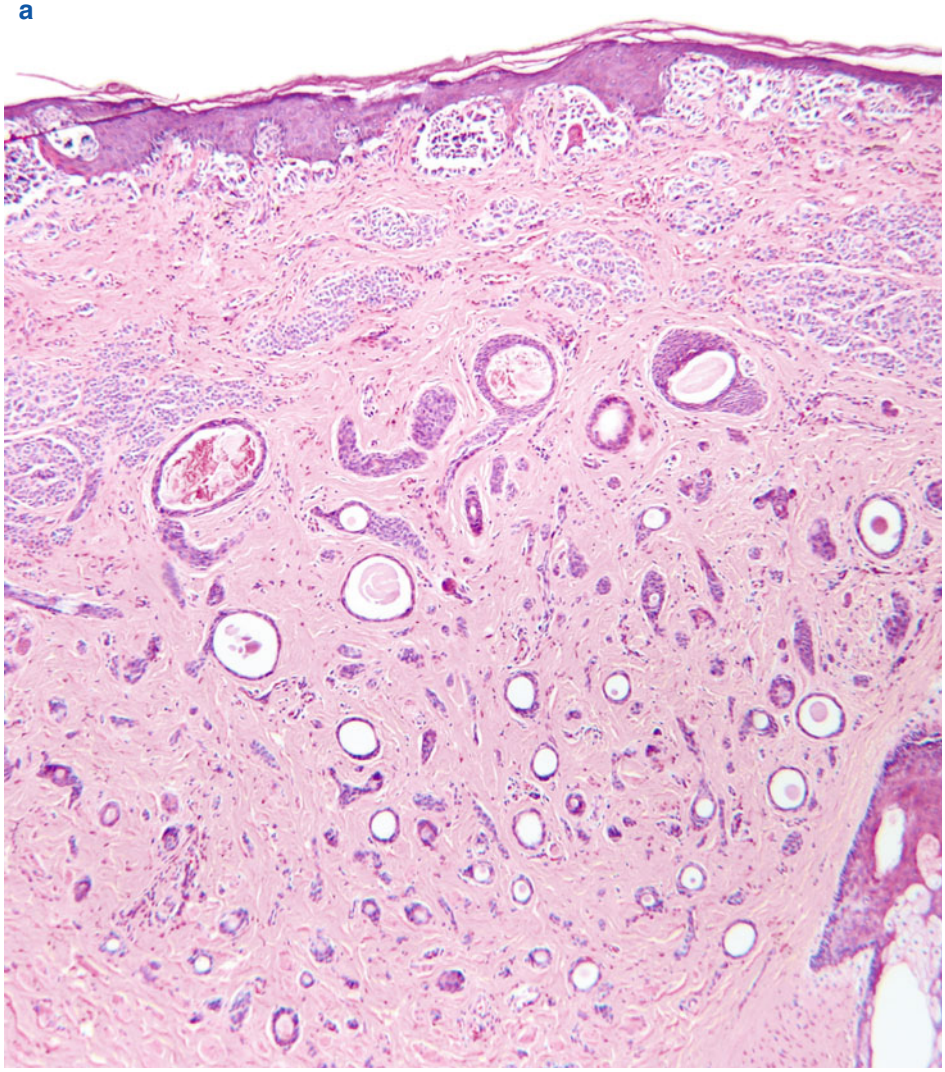


Fig. 5.8
Compound "flat" nevus of the axilla combined with syringoma

*The cells of this nevus are intermingled with short cords of epithelial cells which undergo ductal differentiation (**a**). A few small cysts have the classical comma-shaped appendices typical of syringoma (**b**).*

Note the irregular pattern of the junctional nests: this is not unusual in nevi excised in the axillary area, as was the case of this nevus (see Chap. 22)



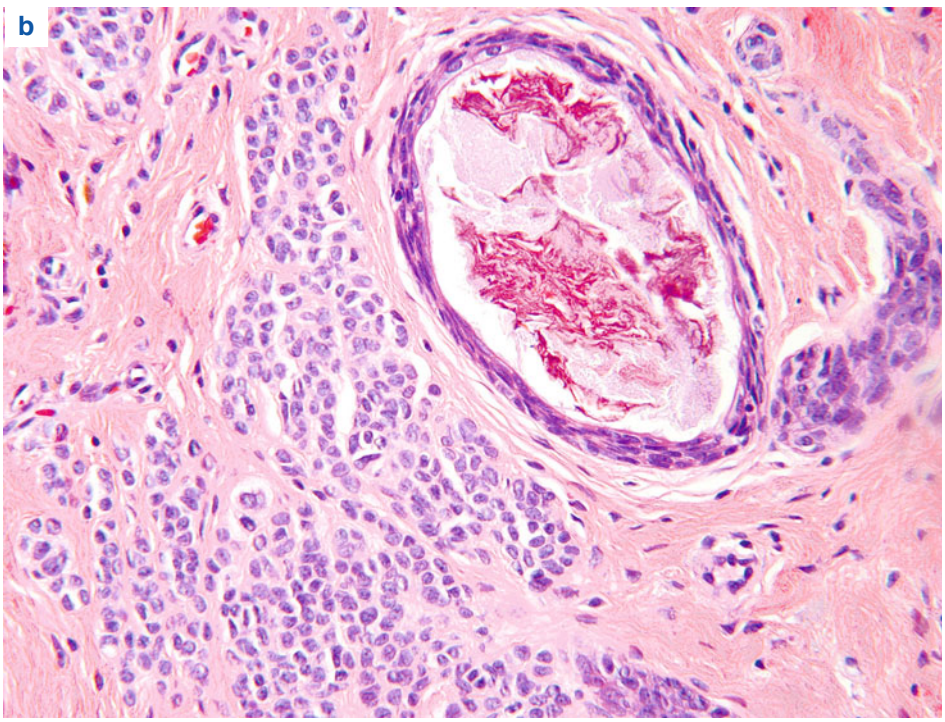


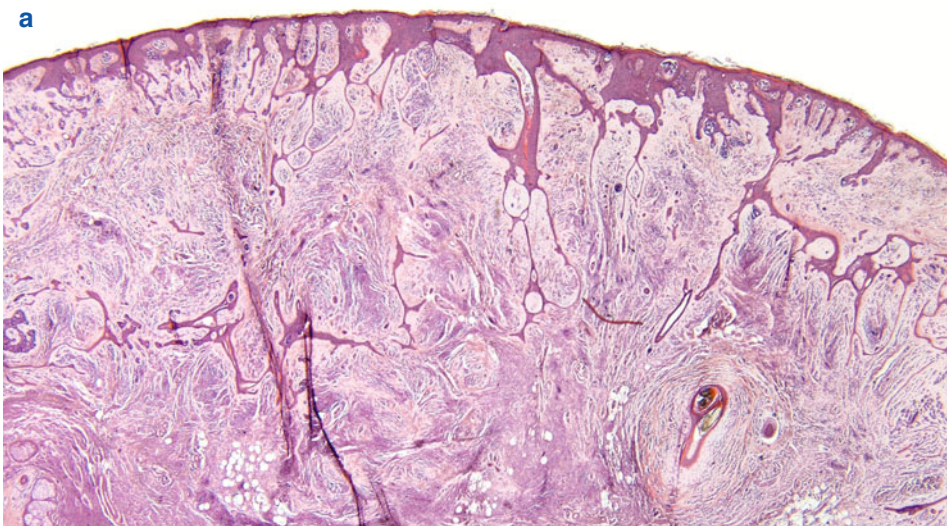
Fig. 5.9
Miescher nevus combined with eccrine syringofibroadenoma

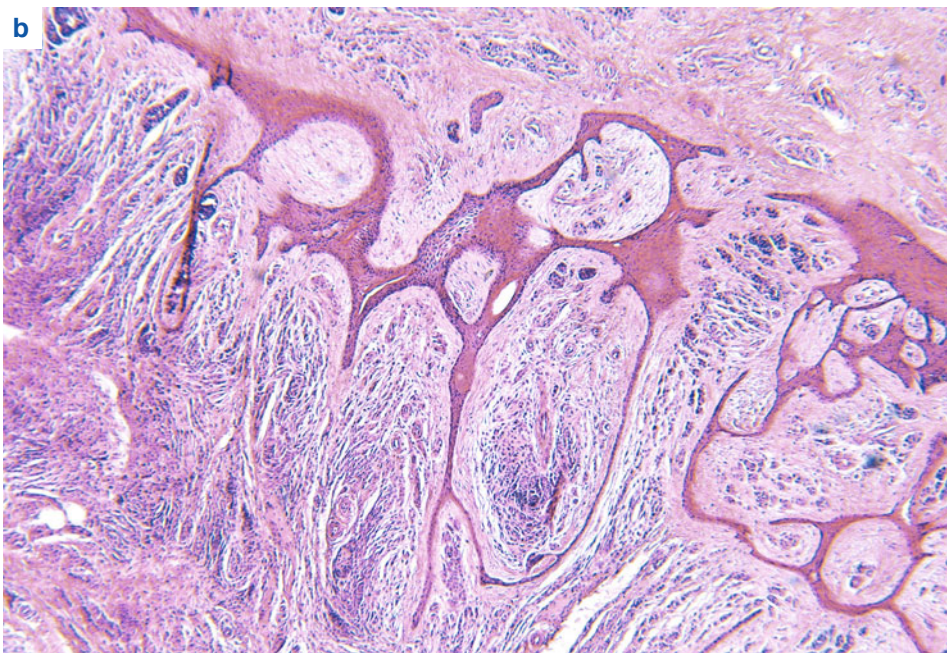
Syringofibroadenoma (acrosyringeal nevus) is a rare condition with a quite variable clinical presentation. In one of its numerous variants, the eccrine ductal proliferation seems to be a reaction to a neoplastic or inflammatory process.

*In this case the long elegant eccrine ducts (**a**) descend from the epidermis and anastomose, entrapping a nevus cells component (**b**). One can also view this proliferation as reactive, e.g., "eccrine syringofibroadenomatosis," provoked by the nevus.*

*The last picture (**c**) shows typical eccrine ductal differentiation with cuticular cells.*

The patient was a 34-year-old woman; the lesion was on her leg





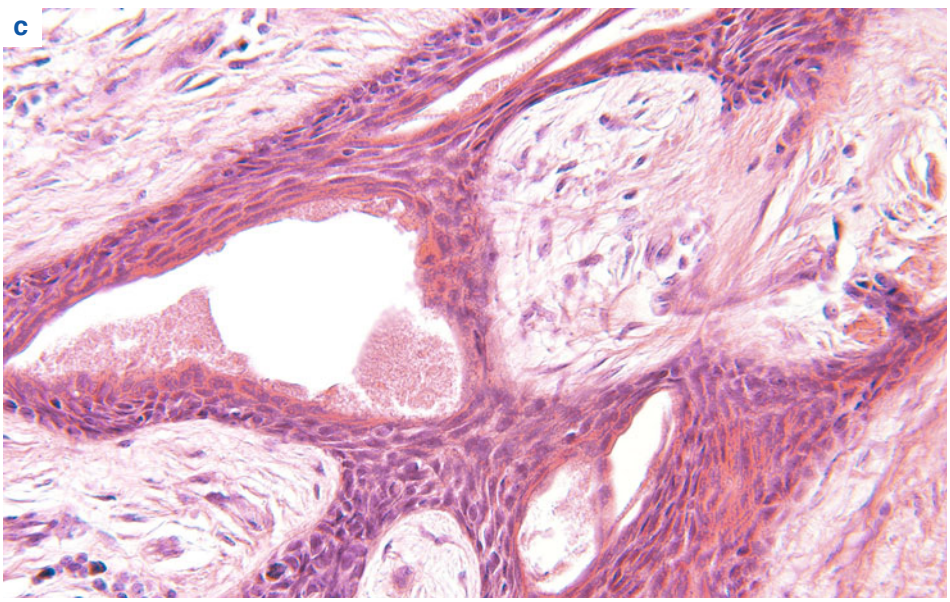
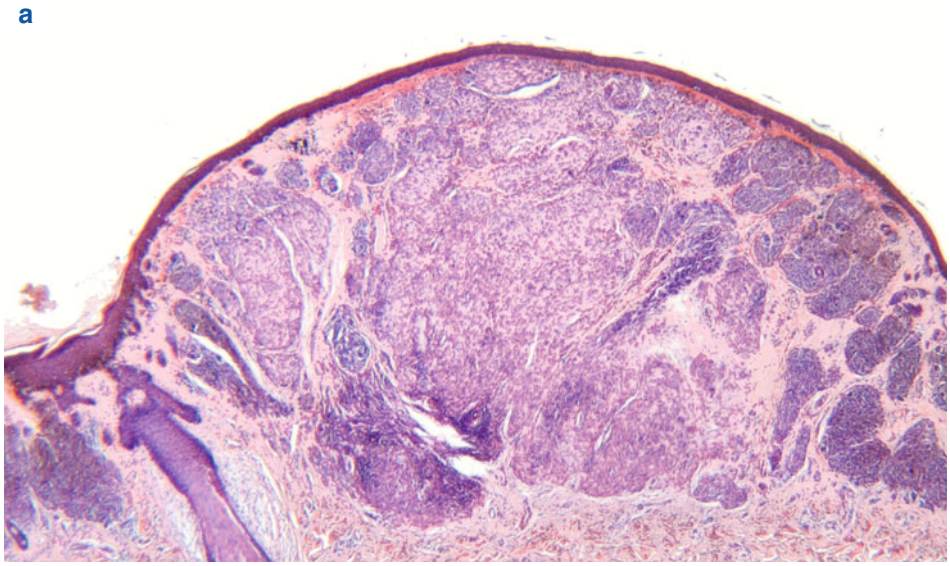


Fig. 5.10
Intradermal Miescher nevus with neural differentiation

*In this case of a nevus with neural differentiation, the similarity with a neural neoplasm is striking, with a neuroma-like picture is evident in the center of the neoplasm (**a**).*

*One might hesitate to make the diagnosis of a nevus because these areas resemble desmoplastic melanoma: the highest magnification picture could have been taken from a case of desmoplastic or neurotropic melanoma or from a melanoma with neural differentiation. However, the area with neural differentiation is lobulated, and the spindled melanocytes are in a fibrillar background, rather than infiltrating between native collagen bundles (**b**). The neural fascicles are similar to those of a benign neural neoplasm, being sharply delineated by clefts and forming a plexiform network.*

Moreover, nests of pigmented benign melanocytes are present above this area and to its sides. Desmoplastic melanoma seldom arises in a nevus and even less frequently beneath one



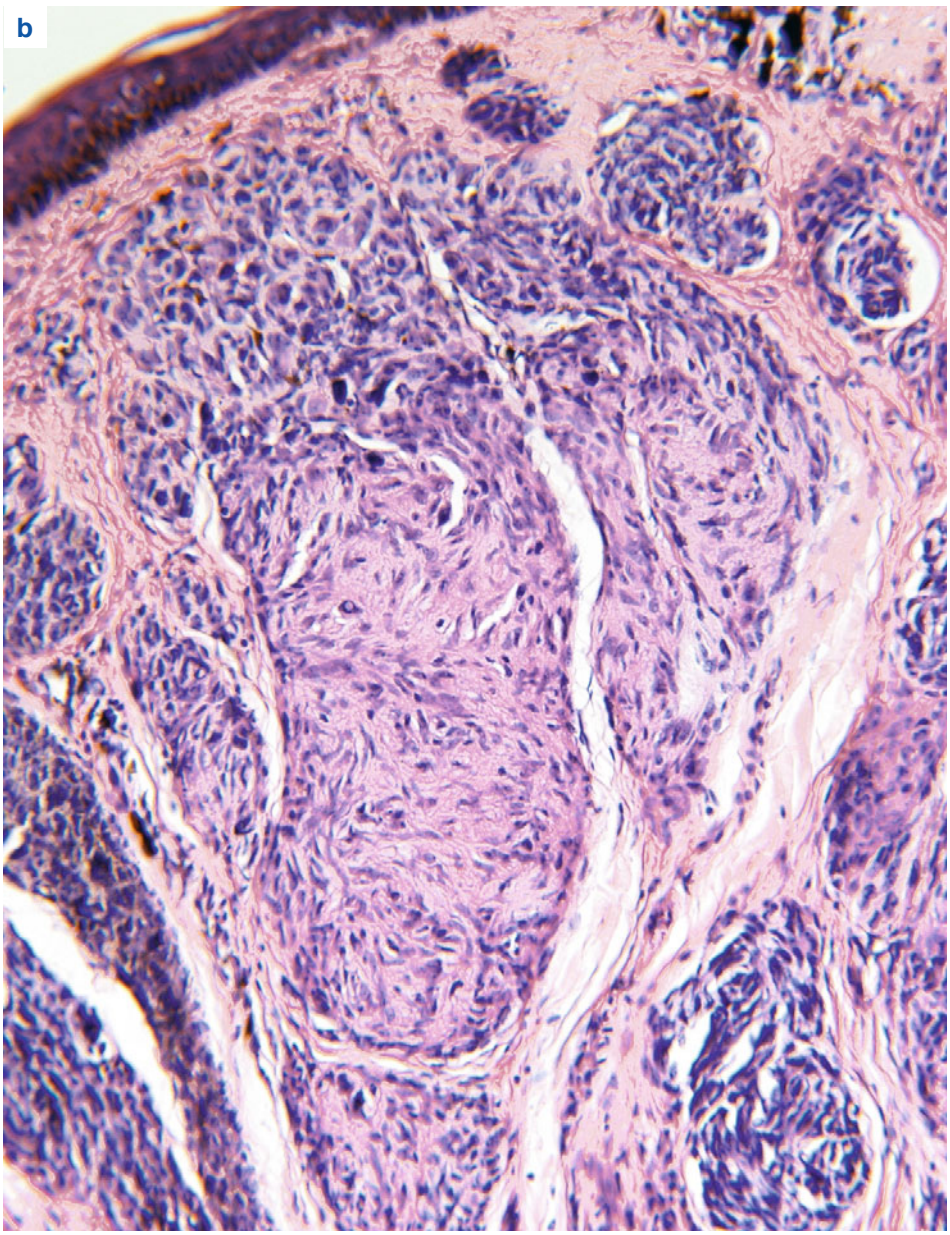


Fig. 5.11
Intradermal nevus with adipocytic metaplasia

*This large neoplasm could be diagnosed as a lipoma or a nevus lipomatosus of Hoffman and Zurhelle (**a**). However, a close scrutiny (and if necessary, immunostaining) reveals the scattered nests that comprise the melanocytic component of this nevus (**b**).*

Notably, some neurofibromas also contain adipocytes, so that small round melanocytes, and not just spindled ones, are required for this diagnosis

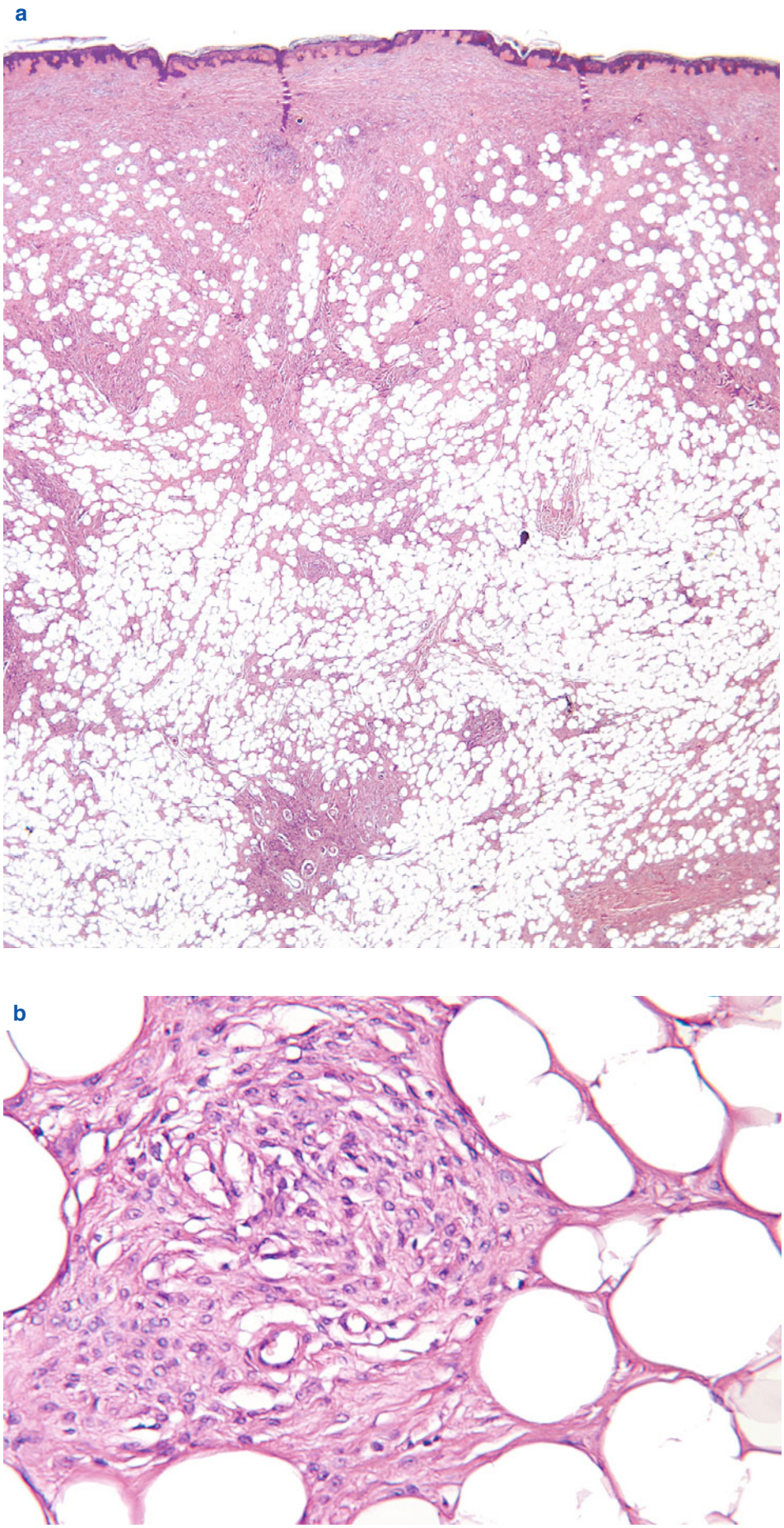
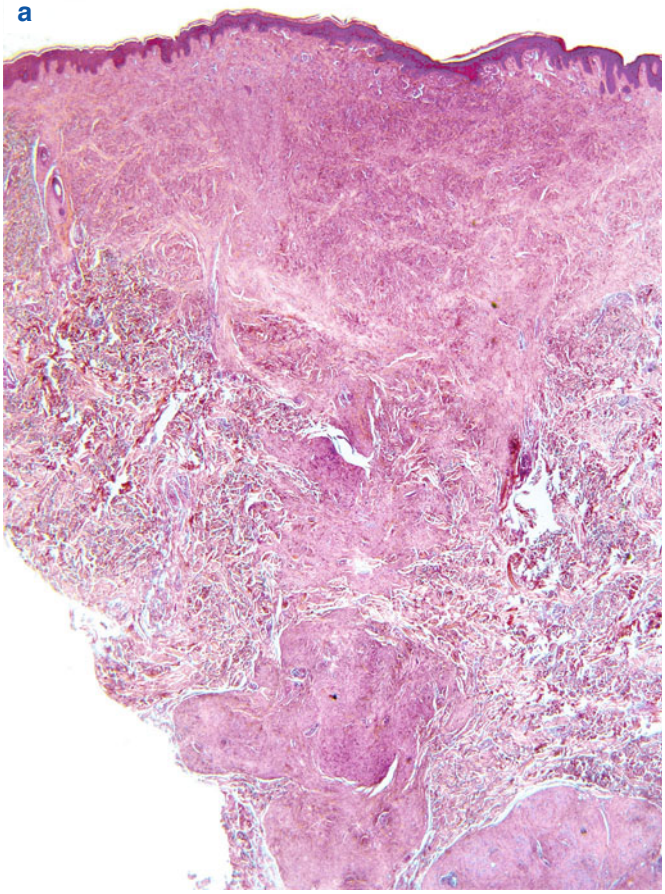


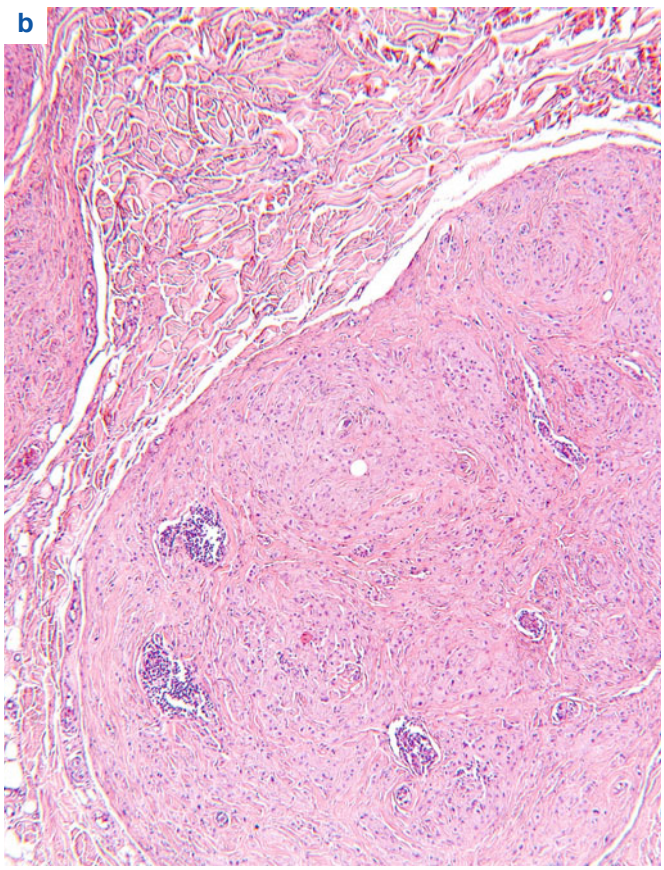
Fig. 5. 12
Desmoplastic (and plexiform) nevus

*In the upper portion of this bizarre lesion, one can easily find the nests of an ordinary common nevus (**a**).*

*The growth pattern in the deep part of the lesion is quite striking. In this part of the lesion, the melanocytes gather to form large cords and are surrounded by a dense collagenous coat (**b**). These large sharp-bordered masses of collagenous nevus are interconnected together to form a plexus.*

*The presence of patently benign melanocytic nests at the top of the lesion rules out desmoplastic melanoma (**c**)*





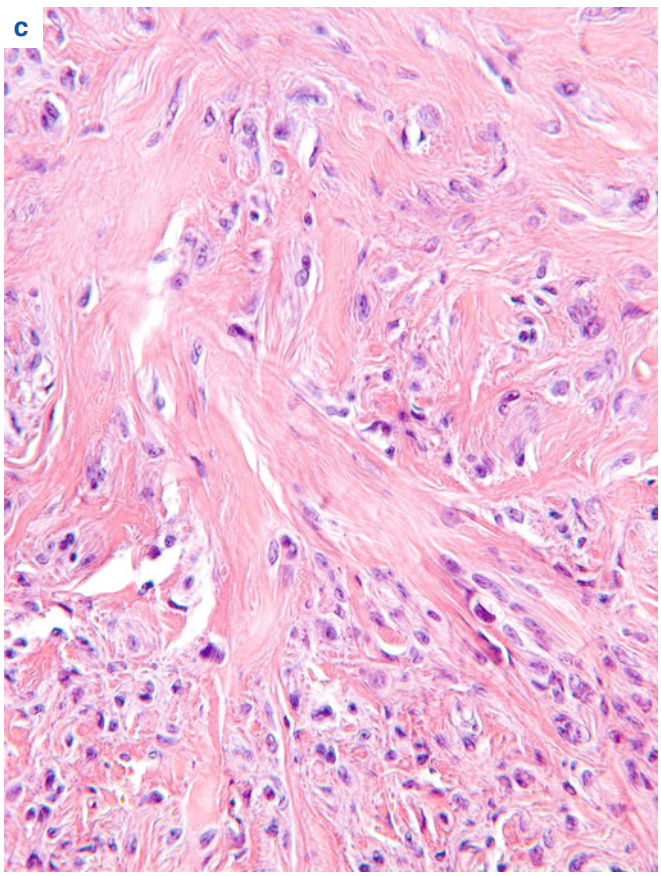


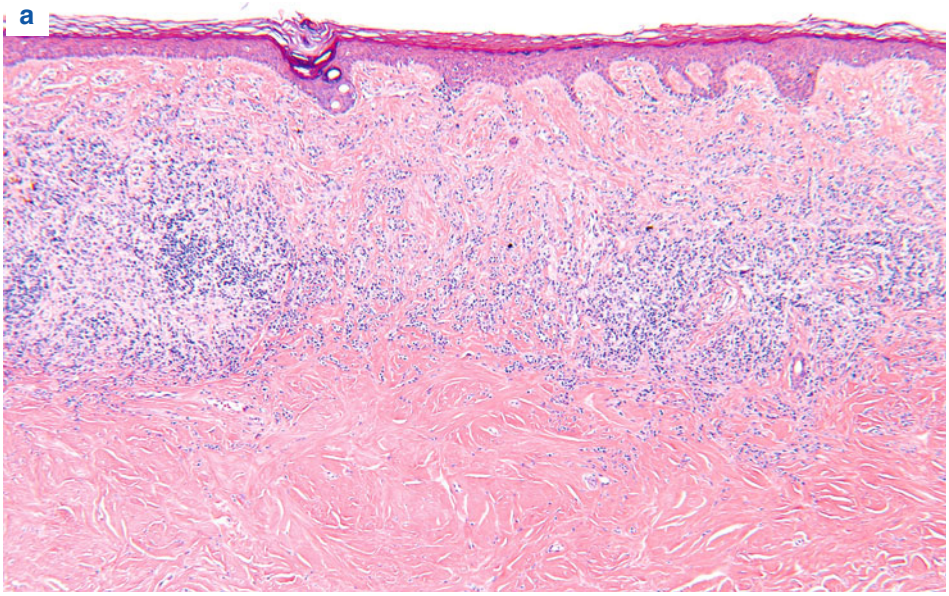
Fig. 5.13
Intradermal desmoplastic nevus

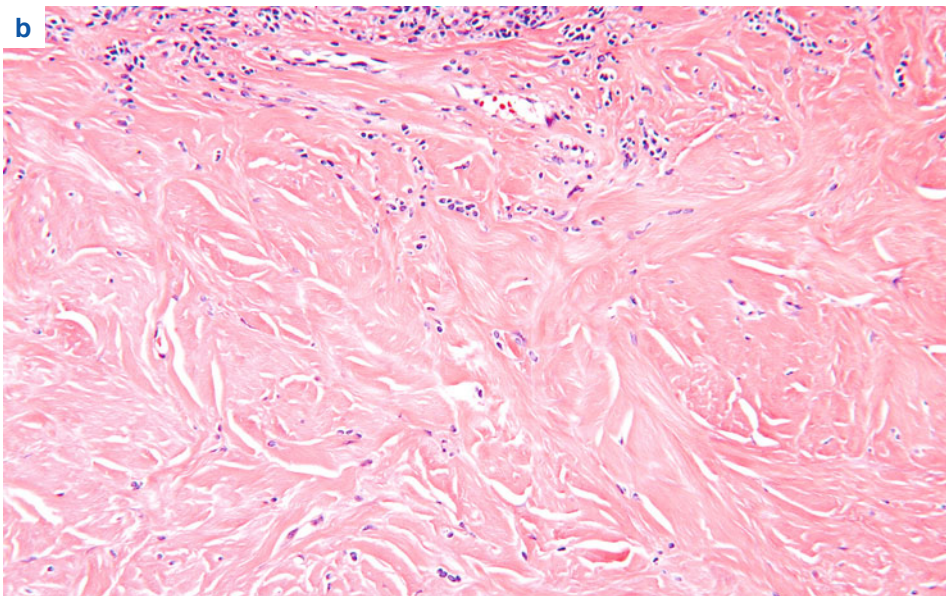
*This peculiar lesion is divided in two components. In the uppermost part of the lesion, there is a nevus cell population gathered in irregular nests or cords (**a**). At the bottom, cells are fewer, roundish, and shrouded in a thick collagenous mantle (**b**, **c**).*

This lesion shows the nearly complete transformation of a nevus into a fibrous neoplasm with large collagen fibers and (myo) fibroblast-like cells, in its deepest portion. At the border between the melanocytic and fibrous components, cells have an intermediate phenotype and a sort of gradient of transformation is distinguishable.

This case is another testimony to the striking plasticity of the melanocytic lineage.

The patient was a 50-year-old female; the lesion was on her foot





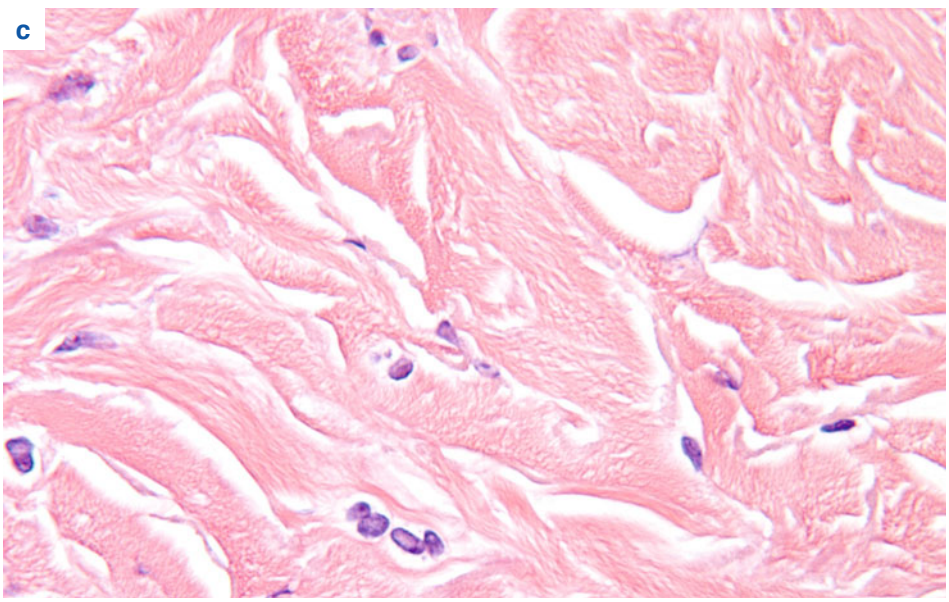


Fig. 5.14
"Hypercellular" "common" nevus

*In routine work we informally call this type of compound nevus with some worrisome characteristics "cellular" or "hypercellular" (**a**). These lesions have a striking cellular density (**b**): cells seem tightly pressed and packed like olives in a jar; nuclei overlap each other and no collagen fibers separate the cells or the nests (which are not evident in this patternless neoplasm). Moreover, the nevus easily reaches the subcutis. This type of lesion is frequently called "minimal deviation melanoma" or "atypical nevus." There is an analogy to proliferative nodules in congenital nevi.*

*However, the lack of mitoses and the strict nuclear monomorphism are both important indications of the entirely benign nature of this peculiar nevus (**c**).*

A lesion like this should be completely excised. This was explicitly recommended in the pathology report, but the patient refused any further procedure. She was a 24-year-old woman and the lesion was situated on her face. No recurrence has been reported for the last 10 years.

If there is any doubt about a lesion such as this one, molecular studies can be employed. This can be especially important if the specimen is not deep enough to see if the melanocytes disperse between collagen bundles at the base of the lesion

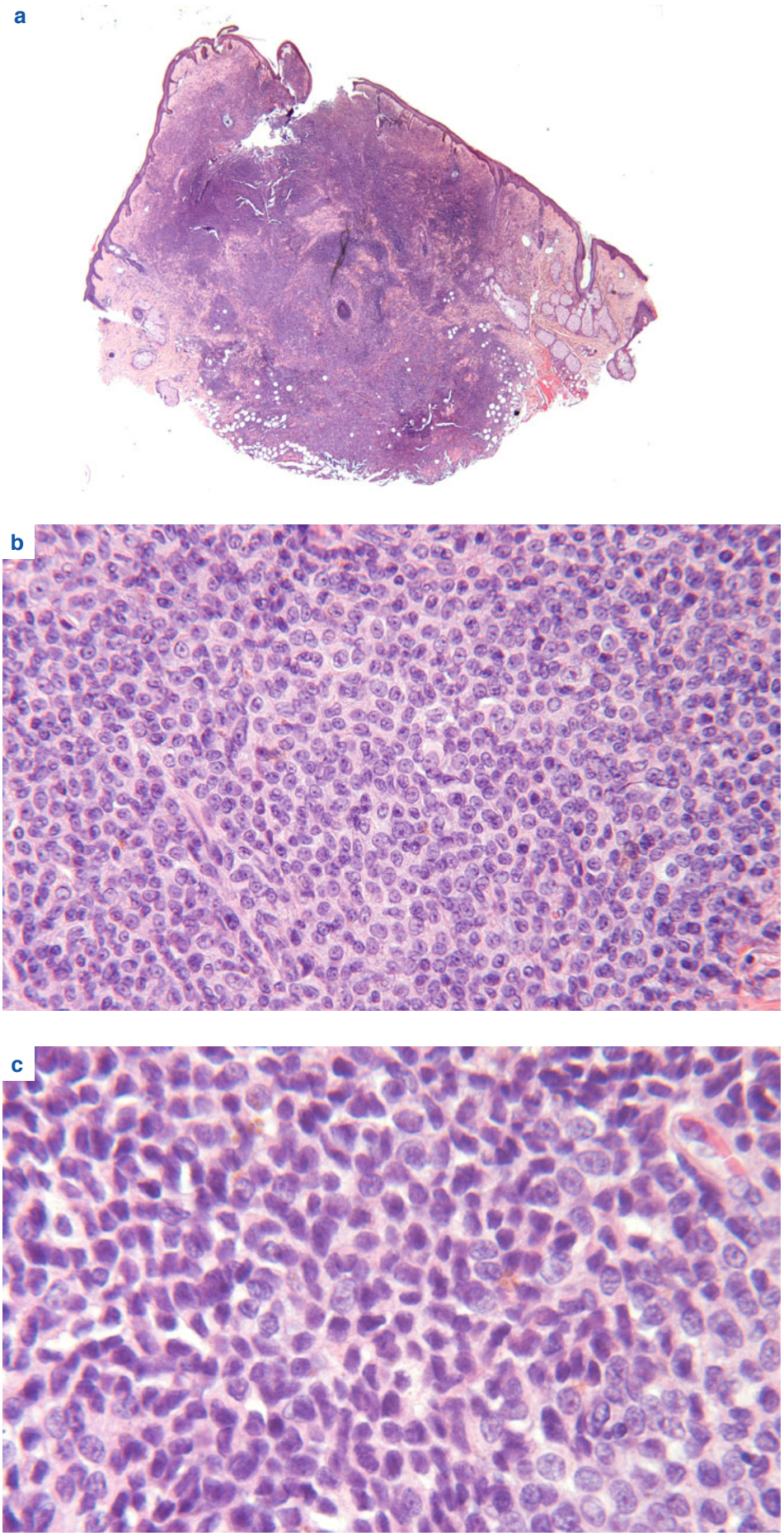
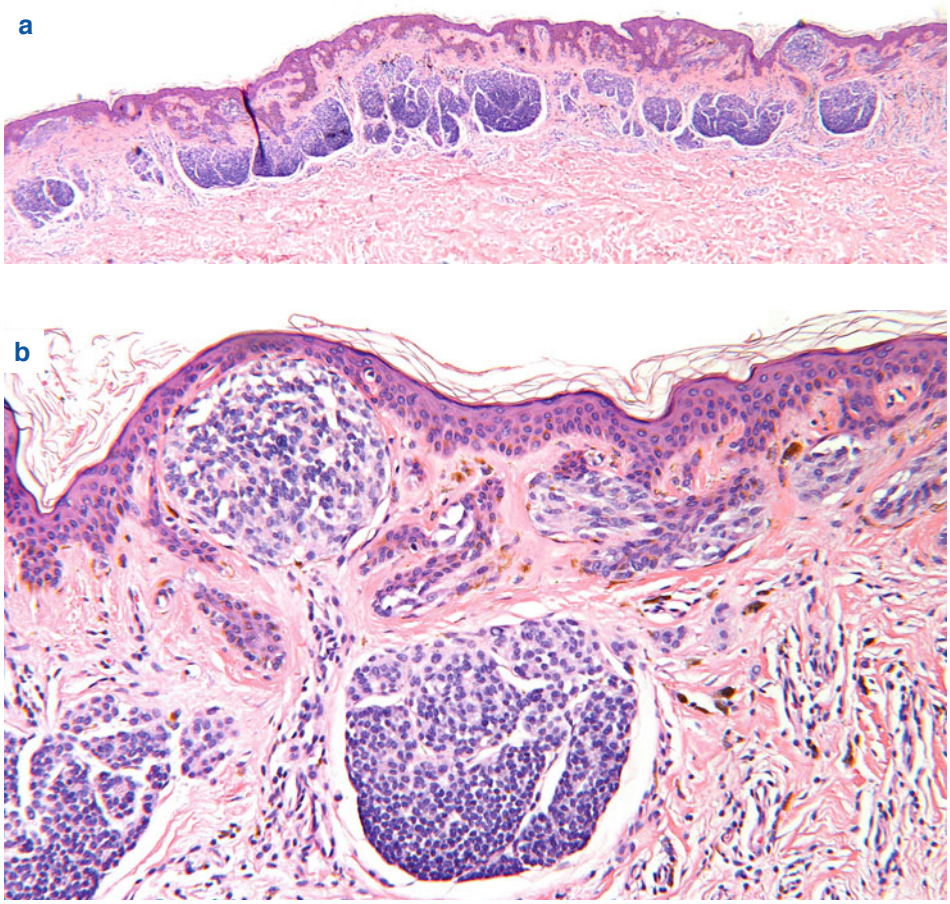


Fig. 5.15
Compound "flat" nevus with large intradermal nests

The widespread use of dermoscopy results in the sampling of nevi with large nests.
*The large expansile nodules can simulate those of a melanoma and careful examination is important (**a**).*

*In this case the innocent-looking cytological details help solve the quandary (**b**). In melanomas with large junctional and intradermal nests, the nuclei are usually atypical. The cytology becomes even more critical when the lesion is in severely sun-damaged skin.*

*Note also that in the last picture as the cells "mature" from the top to the bottom of the nest. Large epithelioid type A melanocytes become small lymphocyte-like type B cells (**c**)*



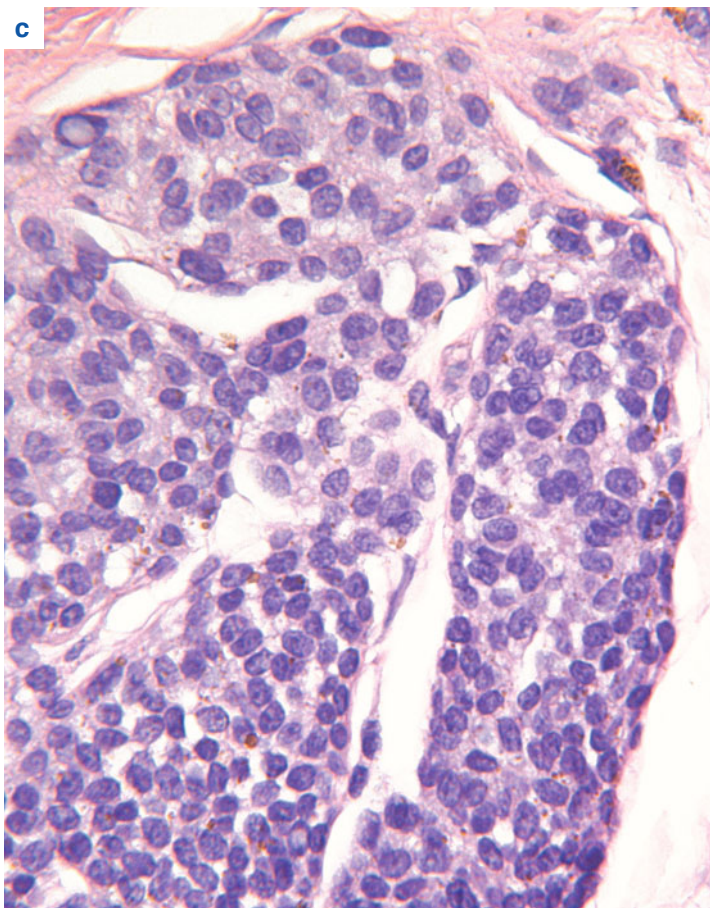
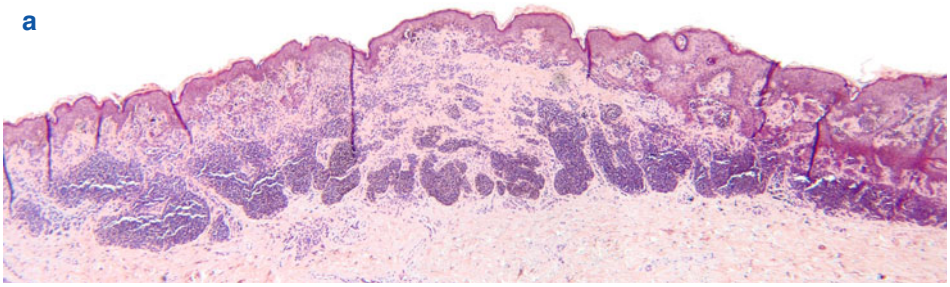
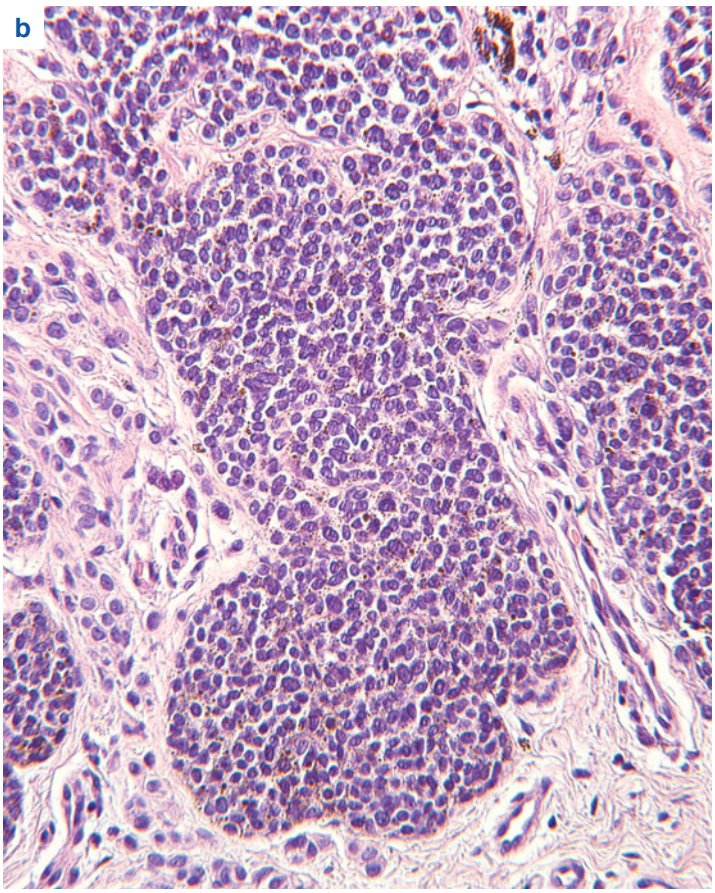


Fig. 5.16
Compound nevus with large intradermal nests

A form of nevoid (or "minimal deviation") melanoma must be always ruled out in lesions with such an atypical silhouette.

Indications of the benign nature of the lesion are:
*- The distribution of the large nests is symmetrical (**a**), and they are evenly distributed throughout the span of the lesional dermis, roughly similar at each tier of the dermis (**b**).*
- Within the nests, atypia and necrosis are absent.
- Mitotic figures are scarce (or nil).
*- There is no significant stromal reaction nor inflammatory infiltrate beneath the nests (**c**).*





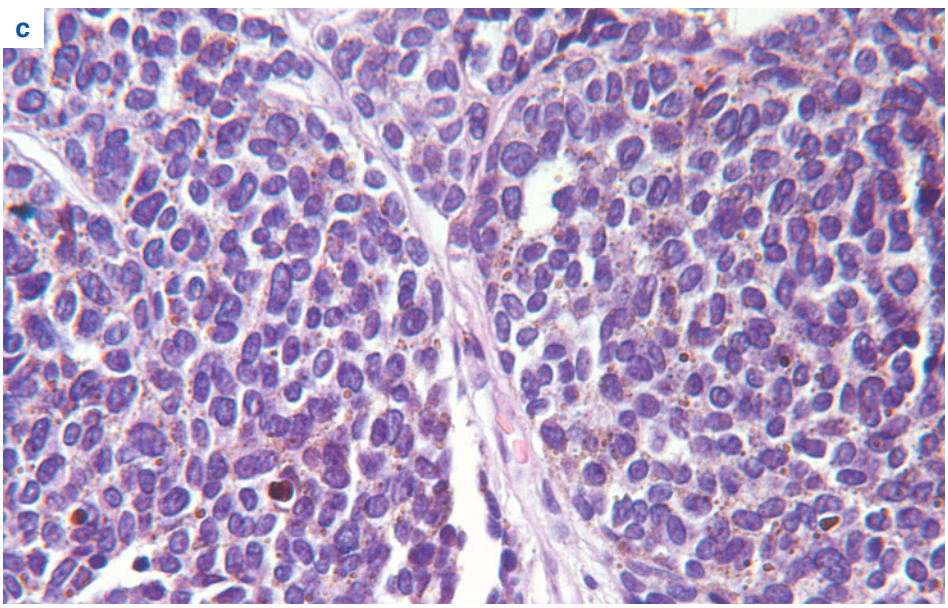


Fig. 5.17
Ancient nevus

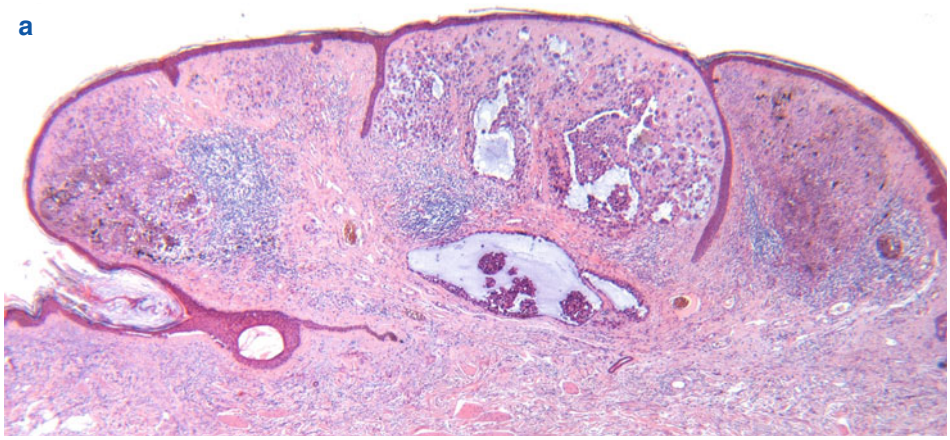
The silhouette of this melanocytic neoplasm is that of an Unna nevus, but a form of polypoid melanoma must be ruled out, and morphological, immunohistochemical, and genetic studies can all play a role in the examination of strange lesions such as this one.

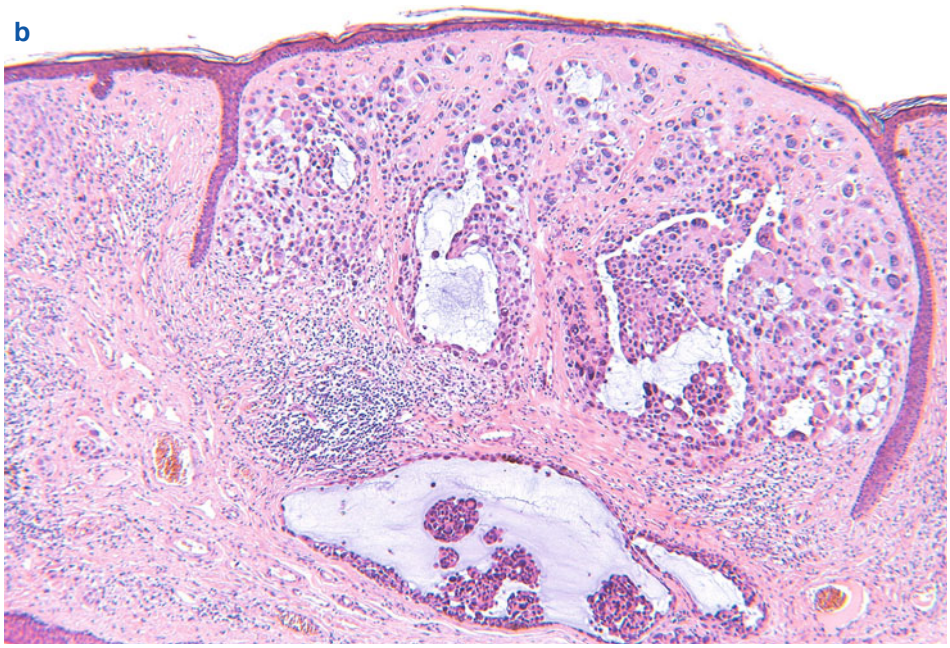
The lesion consists of two components:
*- An area of common nevus is present on the right site (**a**). Here the cells are quite monomorphous and typical, and pigment is evenly distributed.*
*- In the center (**b**), a quite different cellular phenotype is present: the lesional melanocytes are large, epithelioid, and atypical monster cells with enormous nuclei are also present. Despite these ominous features, no mitoses can be found nor necrosis or solid sheets of cells.*

Peculiar details are also present inside the most alarming central component:
- Thick collagen fibers
*- A large pool of mucin (**c**)*
- Sclerotic vessels

All these findings put together indicate that the lesion is not a melanoma but a nevus with senescence-induced cytological alterations. It may be that vascular insufficiency induces the bizarre appearance of the melanocytes (as in pseudosarcomatous decubitus fascitis) and also accounts for the stromal alterations.

(An alternative diagnosis would reasonably be that of a proliferative nodule with spitzian features in a long-lasting congenital nevus)





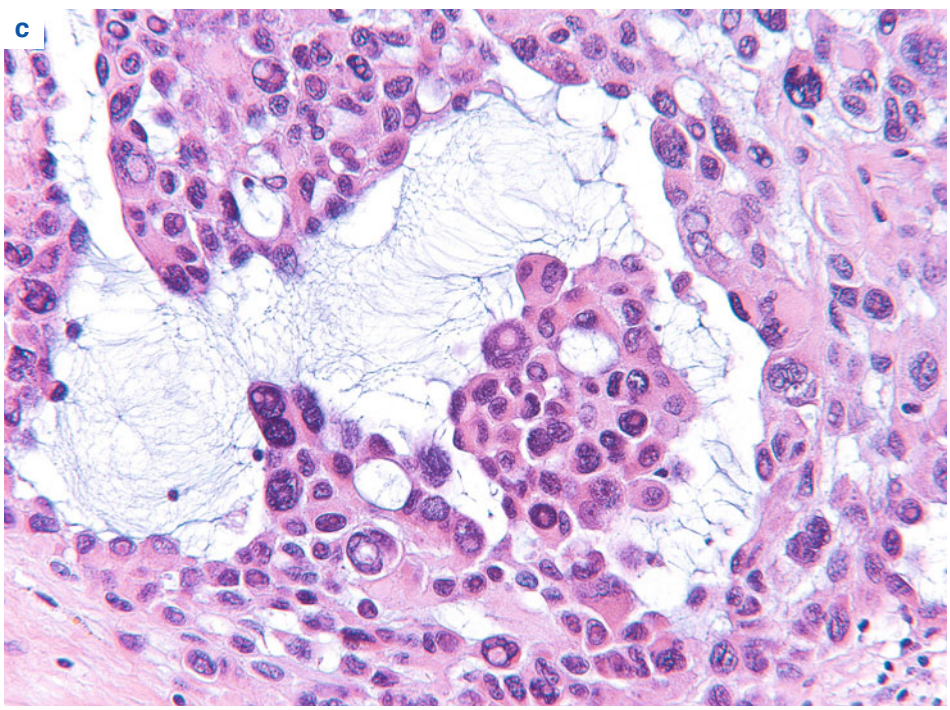


Fig. 5.18
Ancient nevus

*Large foci of extravasated erythrocytes are present in the dominant central nodule in this lesion (**a**).*
*The nodule is composed of large, epithelioid melanocytes (**b**), with some hyperchromatic nuclei. Mitotic figures are rare (**c**).*

Ancient nevi, like ancient neural tumors, often have vascular changes: hyalinized vessel walls, thrombi, or cuffs of perivascular edema.

One is tempting to infer that ischemia plays a role in the bizarre cytomorphology, just as it does in some other conditions (e.g., ischemic fascitis)

(Case kindly provided by H. Kerl, Graz, Austria)

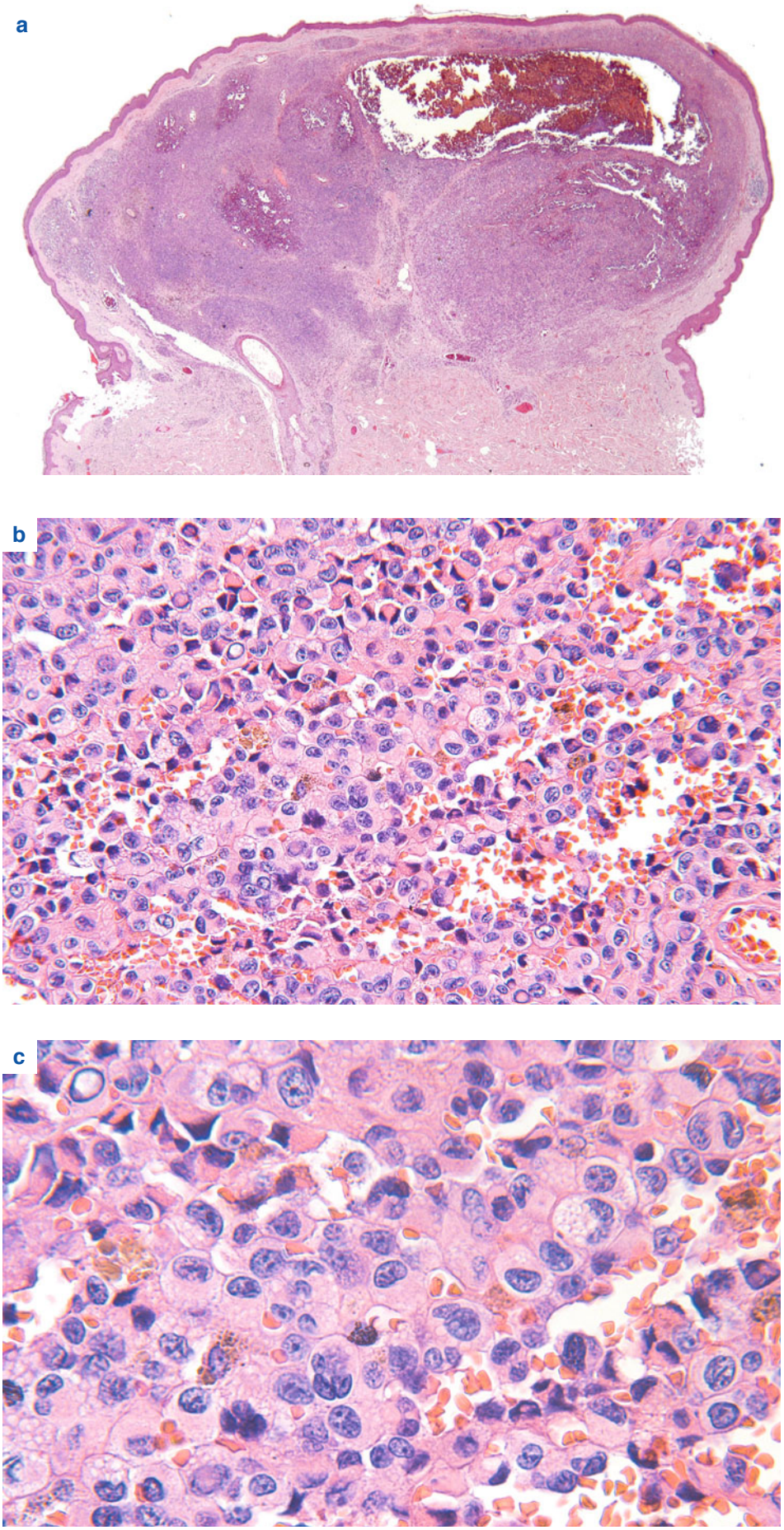


Fig. 5.19
Bizarre nevus
(nevus with monster cells)

This case was sent in consultation to one of us for its strikingly atypical cytological features. Cells are deeply distorted and nuclei are enlarged, irregularly shaped, and diffusely hyperchromatic. These alterations do not seem imputable to artifact because the epidermal and adnexal epithelial cells do not show the same details.

We interpreted the lesion as benign after the following considerations:
*- At the top (**a**) regular junctional nests are present.*
- The atypical portion of the lesion is separate from its junctional component.
*- The large atypical melanocytes are a minority in any high-power field, as they are in a background of small melanocytes (**b**).*
- No mitotic figures nor necrosis is present.
*- Dermal structures are undisturbed (**c**).*

We suggested a complete removal of the lesion which showed Miescher-type or congenital features. Three years follow-up was negative for recurrence or metastases

(Case kindly provided by A. R. Lombardi Rimini, Italy)

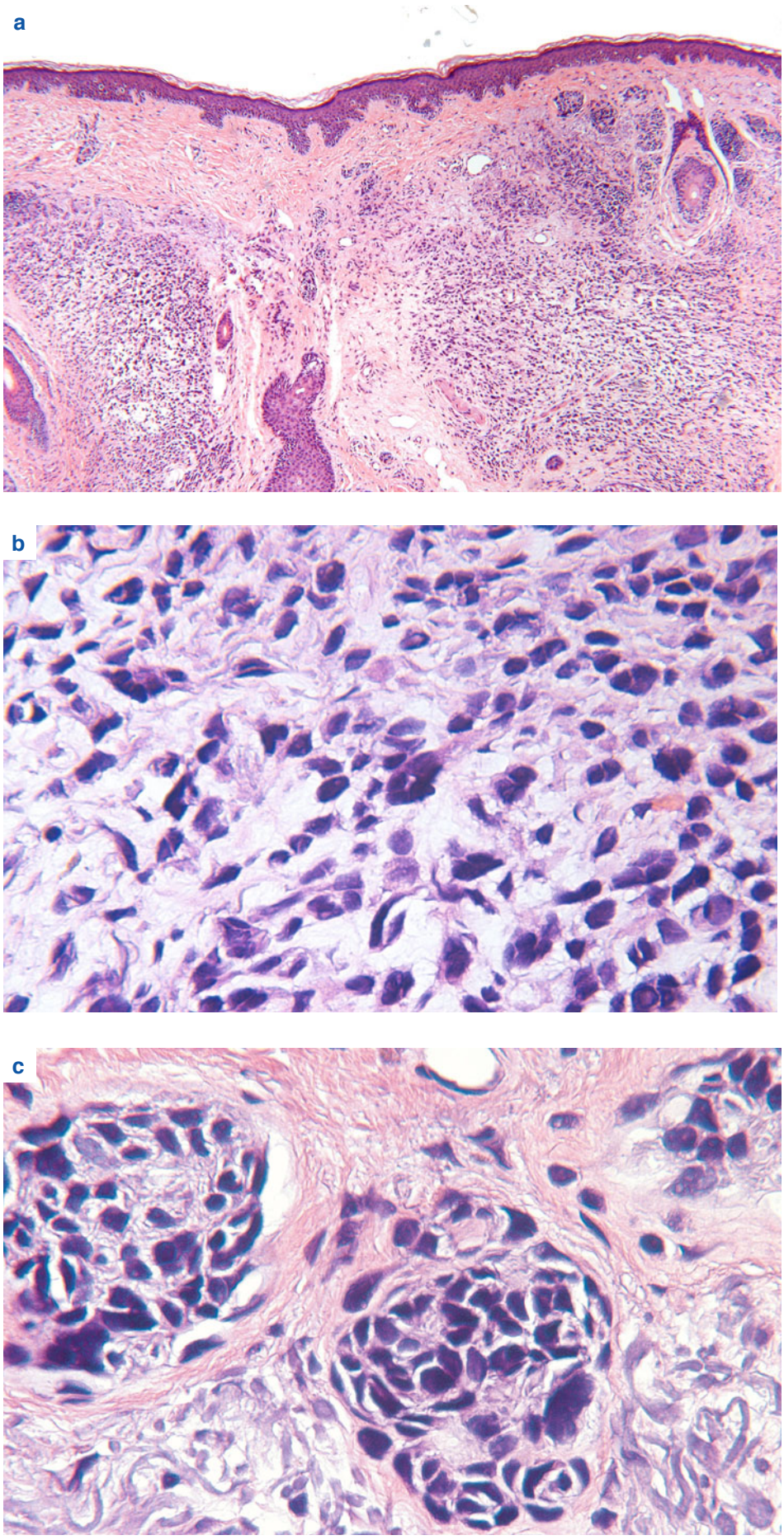


Fig. 5.20
Bizarre nevus
(nevus with monster cells)

*The very same type of cells as in the previous case of Fig. 5.19 is present here (**a**). In this lesion however a more extensive benign, banal-looking nevus cell component is also present and makes the diagnosis easier (**b**).*

*In cases with monster cells like those pictured in these pages, one must always rule out an intradermal melanoma or a melanoma that has developed in the intradermal portion of a nevus. The smudgy chromatin in the larger cells is an important detail (**c**).*

Ki-67 immunostain provided less than 2% positive cells.

This lesion was excised from the face of a 67-year-old woman

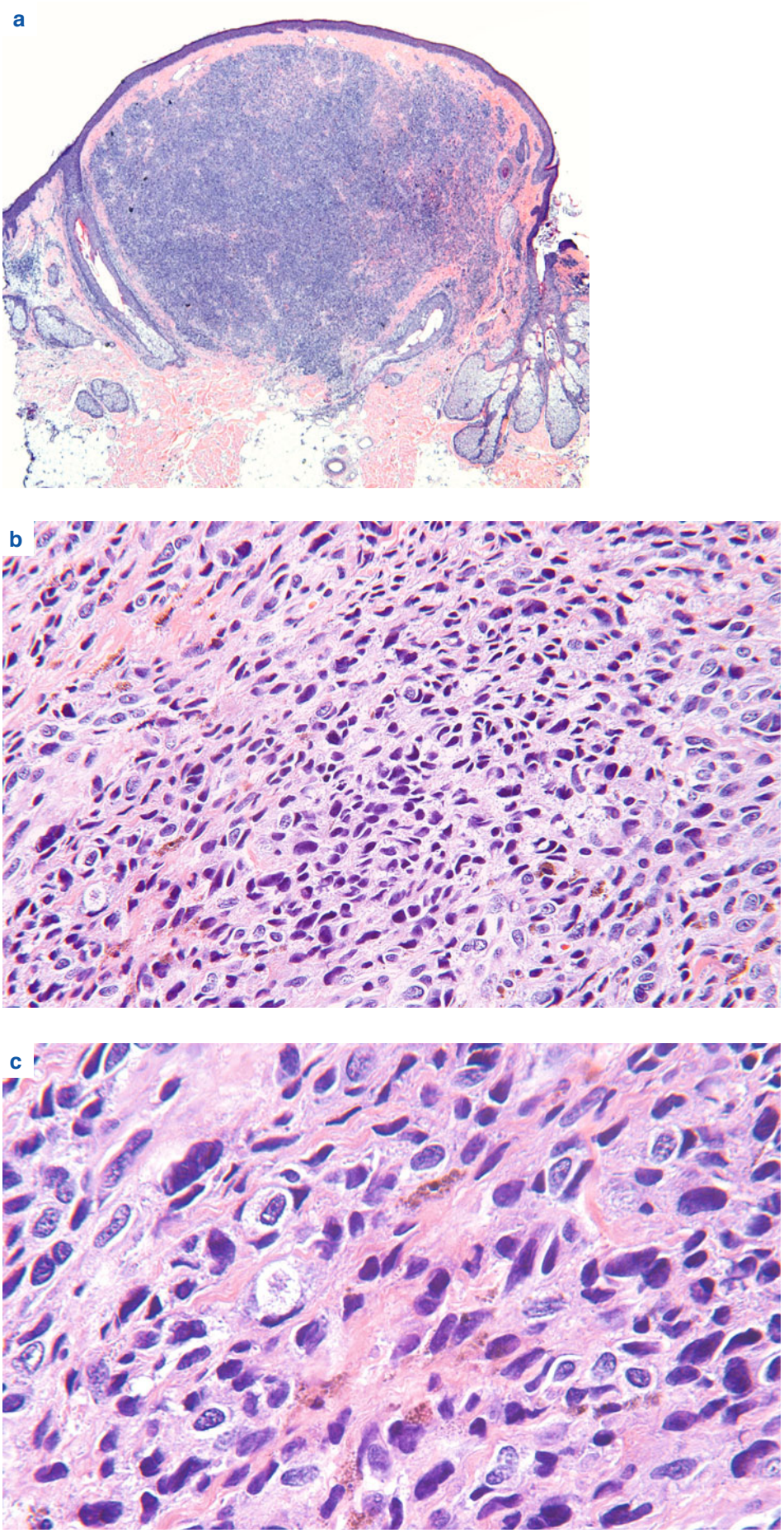


Fig. 5.21
Nevus with eosinophilic intranuclear inclusions

Pseudonuclear inclusions are quite frequent in nevi and melanoma. They are due to invagination of a knuckle of cytoplasm inside the nucleus; when sectioned, a round space that stains lighter than the rest of the nucleus appears.

*Bona fide intranuclear inclusions are on the contrary exceptional (**a**), and only few cases have been reported.*

*The differential diagnosis would include the so-called rhabdoid melanoma, but the architecture and the cytology of the lesion exclude malignancy (**b**, **c**)*

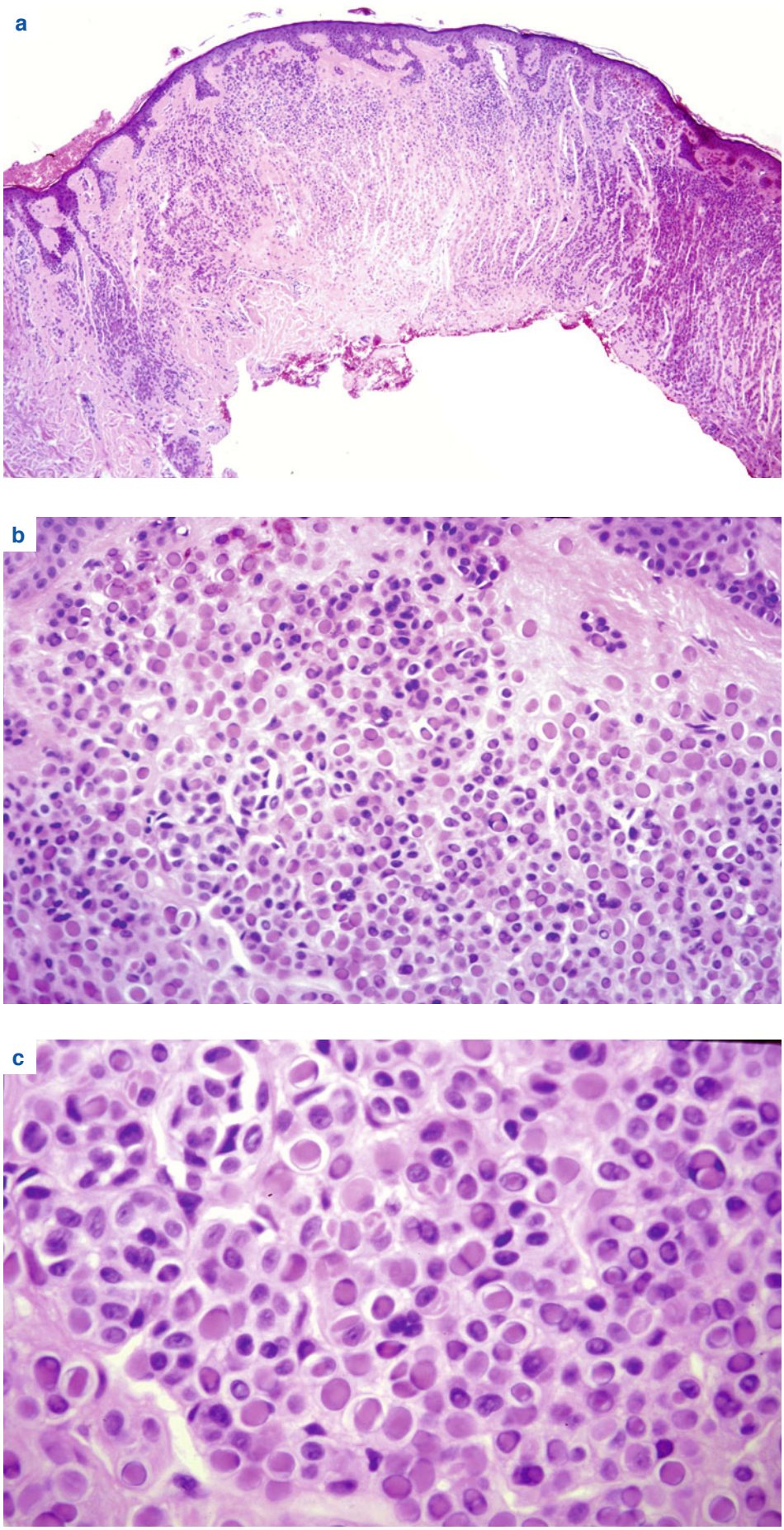
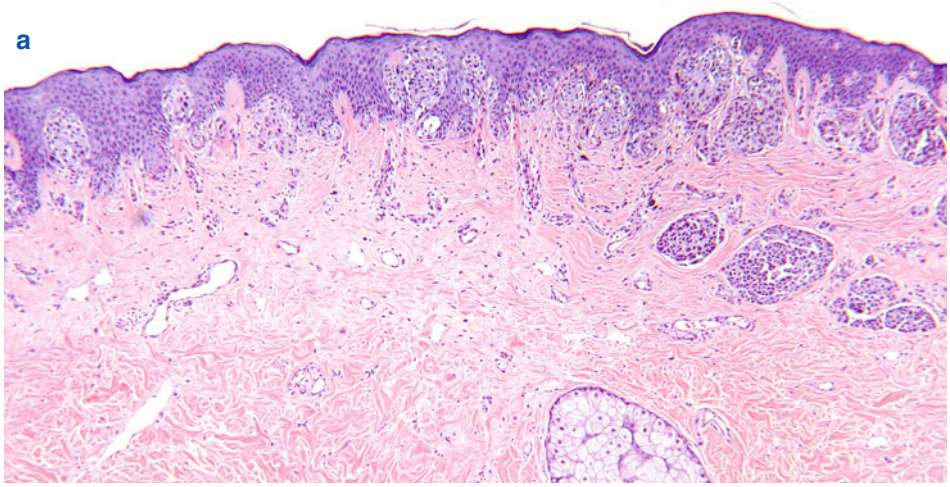


Fig. 5.22
Compound "flat" nevus with vacuolated cells ("pagetoid cells")

*Large cells with pale, vacuolated cytoplasm mostly compose this compound, partially regressed, melanocytic neoplasm (**a**). Ackerman, who noted their resemblance to those of Paget disease, called these cells "pagetoid melanocytes." This reference is confusing, as pathologists are more familiar with the use of the term pagetoid to connote upward migration.*

The architectural features of this nevus are those of a Clark or dysplastic one.
The differential diagnosis is with a mostly nested melanoma with which it has many features in common.
*The monomorphic nature of the nuclei is helpful (**b**). Immunoperoxidase staining for Ki-67 and, if necessary, molecular techniques can be used in the most difficult cases in which this diagnosis is considered.*

The patient was a 28-year-old female and the lesion was on her breast



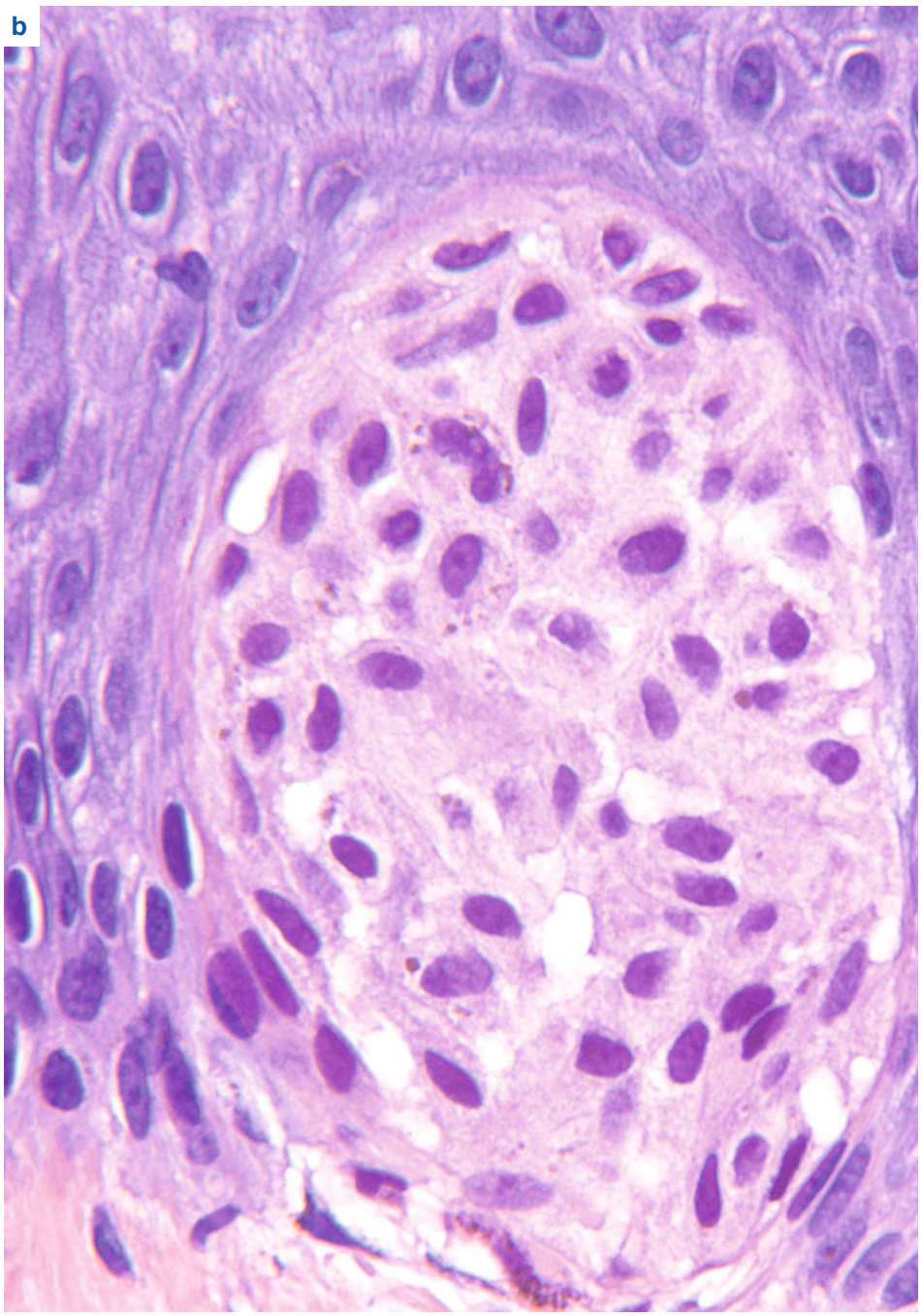


Fig. 5.23
Balloon cell nevus

*This large nevus with congenital features consists of two components: at the top the tissue of an ordinary nevus is present (**a**), while in the subjacent reticular dermis, balloon cells dominate (**b**).*

*Note the small size and the uniform diameter of the nuclei (**c**). This feature along with the absence of mitoses is an important clue to the benign nature of the lesion.*

The large empty spaces between the edge of some of the melanocytes of the nevus and adjacent collagen bundles are caused by rupture of vacuolated organelles and by retraction after fixation.

The lesion was on the cheek of a 20-year-old woman